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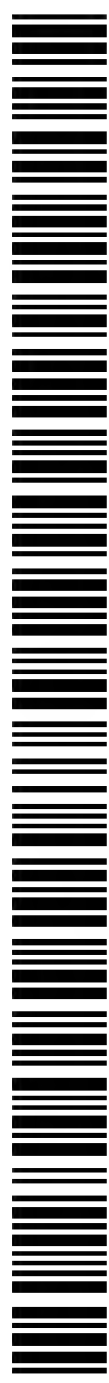
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(54) Title: UREA DERIVATIVES AS KINASE MODULATORS

(57) Abstract: The invention provides methods and compositions for treating conditions mediated by various kinases wherein derivatives of urea compounds are employed. The invention also provides methods of using the compounds and/or compositions in the treatment of a variety of diseases and unwanted conditions in subjects.



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UREA DERIVATIVES AS KINASE MODULATORS

This application claims priority to US Provisional Application No. 60/520,273, filed November 13, 2003, US Provisional Application No. 60/527,094, filed December 3, 2003, US Provisional Application No. 60/531,243, filed December 18, 2003, and US Provisional Application No. 60/531,082, filed December 18, 2003, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND

Protein kinases (PKs) play a role in signal transduction pathways regulating a number of cellular functions, such as cell growth, differentiation, and cell death. PKs are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins, and can be conveniently broken down into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs). Growth factor receptors with PTK activity are known as receptor tyrosine kinases. Protein receptor tyrosine kinases are a family of tightly regulated enzymes, and the aberrant activation of various members of the family is one of the hallmarks of cancer. The protein-tyrosine kinase family, which includes Bcr-Abl tyrosine kinase, can be divided into subgroups that have similar structural organization and sequence similarity within the kinase domain. The members of the type III group of receptor tyrosine kinases include the platelet-derived growth factor (PDGF) receptors (PDGF receptors α and β), colony-stimulating factor (CSF-1) receptor (CSF-1R, c-Fms), FLT-3, and stem cell or steel factor receptor (c-kit). A more complete listing of the known Protein receptor tyrosine kinases subfamilies is described in Plowman et al., DN&P, 7(6):334-339 (1994), which is incorporated by reference, including any drawings, as if fully set forth herein. Furthermore, for a more detailed discussion of "non-receptor tyrosine kinases", see Bolen, Oncogene, 8:2025-2031 (1993), which is incorporated by reference, including any drawings, as if fully set forth herein.

Hematologic cancers, also known as hematologic or hematopoietic malignancies, are cancers of the blood or bone marrow; including leukemia and lymphoma. Acute myelogenous leukemia (AML) is a clonal hematopoietic stem cell leukemia that represents ~90% of all acute leukemias in adults. See e.g., Lowenberg et al., *N. Eng. J. Med.* 341:1051-62 (1999). While chemotherapy can result in complete remissions, the long term disease-free survival rate for AML is about 14% with about 7,400 deaths from AML each year in the

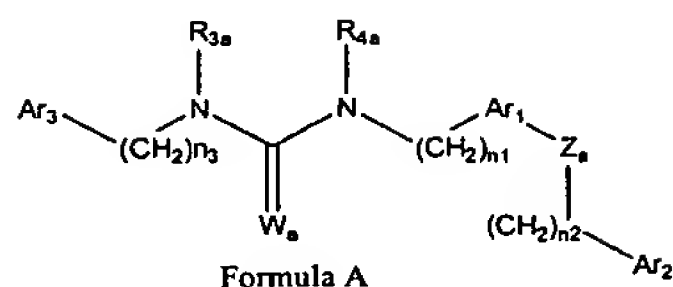
The compounds provided by the present invention are urea derivatives of substituted aryls and hetroaryls, e.g., isoxazoles, pyrazoles and isothiazoles. Urea derivatives of pyrazoles have been reported to be selective p38 kinase inhibitors by Dumas, J., et al., *Bioorg. Medic. Chem. Lett.* 10:2051-2054 (2000). Oxazoles and isopyrazoles are suggested as blockers of cytokine production in WO 00/43384 published 27 July 2000. Urea derivatives of isoxazole and pyrazoles are described as inhibitors of RAF kinase in WO 99/32106 published 1 July 1999. Such compounds are also described as p38 kinase inhibitors by Dumas, J., et al., *Bioorg. Medic. Chem. Lett.* 10:2047-2050 (2000). These compounds are also suggested as p38 kinase inhibitors in PCT publication WO 99/32111 published 1 July 1999.

There remains a need for additional compounds that are effective in inhibiting kinase activity. Given the complexities of signal transduction with the redundancy and crosstalk between various pathways, the identification of specific kinase inhibitors permits accurate targeting with limited inhibition of other pathways, thus reducing the toxicity of such inhibitory compounds.

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The present invention provides compounds which modulate kinase activity, and in some embodiments inhibit protein tyrosine kinases or a specific kinase or kinase class. In some embodiments, the compositions and methods for treating and preventing conditions and diseases, such as cancer, hematologic malignancies, cardiovascular disease, inflammation or multiple sclerosis. The compounds of the invention can be delivered alone or in combination with additional agents, and are used for the treatment and/or prevention of conditions and diseases. As used throughout the specification, unless otherwise stated, each of the substituents is as previously defined.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the structure:



wherein:

- (a) R_{3a} and R_{4a} are each a suitable substituent independently selected from hydrogen, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer, preferably from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH₂, -NHC(NH)NH₂, -C(S)NH₂, -NHC(S)NH₂, -NHC(O)NH₂, -S(O₂)H, -S(O)H, -NH₂, -C(O)NH₂, -OC(O)NH₂, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O₂)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO₂C(O)OH, -NHSH, -NHS(O)H, -NHSO₂H, -C(O)SH, -C(O)S(O)H, -C(O)S(O₂)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO₂)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO₂)H, -S(O₂)NH₂, -S(O)NH₂, -SNH₂, -NHCS(O₂)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of halogens, =O, -NO₂, -CN, -(CH₂)_z-CN where z is a whole integer, preferably from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c-, C(O)NR_c, -C(O)OR_c, -C(O)R_c, -NR_cC(O)NR_cR_c-, -NR_cC(O)R_c, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group; or where R_{3a} and R_{4a} together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with one or more suitable substituents selected from

halogen, =O; =S; -CN; -NO₂, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer, preferably from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH₂, -NHC(NH)NH₂, -C(S)NH₂, -NHC(S)NH₂, -NHC(O)NH₂, -S(O₂)H, -S(O)H, -NH₂, -C(O)NH₂, -OC(O)NH₂, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O₂)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO₂C(O)OH, -NHSH, -NHS(O)H, -NHSO₂H, -C(O)SH, -C(O)S(O)H, -C(O)S(O₂)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO₂)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO₂)H, -S(O₂)NH₂, -S(O)NH₂, -SNH₂, -NHCS(O₂)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of halogens, =O, -NO₂, -CN, -(CH₂)_z-CN where z is a whole integer, preferably from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -NR_cC(O)NR_cR_c, -NR_cC(O)R_c, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

(b) Ar₁, Ar₂ and Ar₃ are each independently an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer, preferably from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH₂, -NHC(NH)NH₂, -C(S)NH₂, -NHC(S)NH₂, -NHC(O)NH₂, -S(O₂)H,

-S(O)H, -NH₂, -C(O)NH₂, -OC(O)NH₂, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H,
 -OS(O₂)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO₂C(O)OH, -NHSH,
 -NHS(O)H, -NH₂SO₂H, -C(O)SH, -C(O)S(O)H, -C(O)S(O₂)H, -C(S)H, -C(S)OH,
 -C(SO)OH, -C(SO₂)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO₂)H, -S(O₂)NH₂,
 -S(O)NH₂, -SNH₂, -NHCS(O₂)H, -NHC(SO)H, -NHC(S)H, and -SH groups

unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of halogens, =O, -NO₂, -CN, -(CH₂)_z-CN where z is a whole integer, preferably from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -NR_cC(O)NR_cR_c, -NR_cC(O)R_c, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

(c) n₁ is 0, 1, 2, 3 or 4;

(d) n₂ is 0, 1, 2, 3 or 4;

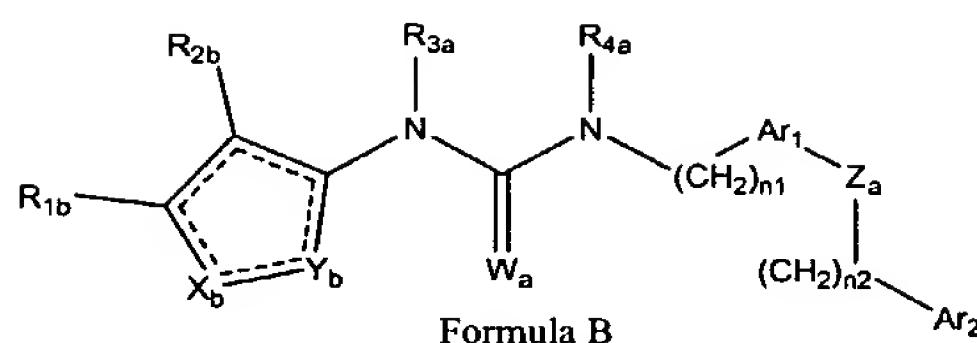
(e) n₃ is 0, 1, 2, 3 or 4;

(f) Z_a is a bond or is selected from S, O, N, NR_c, C(O)NR_c, NR_cC(O), and CR_c, wherein R_c is a suitable substituent selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl group; and

(g) W_a is S or O;

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, isomer derivative, or pharmaceutically acceptable solvate thereof.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the structure:

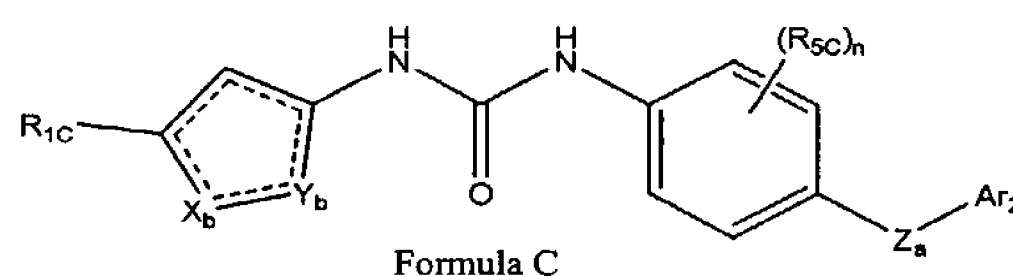


wherein:

- (a) X_b and Y_b are independently selected from O, N, NR_{c1} , and CR_c , wherein R_{c1} is a suitable substituent selected from hydrogen; alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl unsubstituted or substituted with one, two, or three suitable substituents, wherein X_b and Y_b are not both oxygen;
- (b) R_{1b} and R_{2b} are each a suitable substituent independently selected from hydrogen, halogen, $=O$; $=S$; $-CN$; $-NO_2$, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of: halogens; $=O$; $=S$; $-CN$; and $-NO_2$; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, $=NH$, $-NHOH$, $-OH$, $-C(O)H$, $-OC(O)H$, $-C(O)OH$, $-OC(O)OH$, $-OC(O)OC(O)H$, $-OOH$, $-C(NH)NH_2$, $-NHC(NH)NH_2$, $-C(S)NH_2$, $-NHC(S)NH_2$, $-NHC(O)NH_2$, $-S(O_2)H$, $-S(O)H$, $-NH_2$, $-C(O)NH_2$, $-OC(O)NH_2$, $-NHC(O)H$, $-NHC(O)OH$, $-C(O)NHC(O)H$, $-OS(O_2)H$, $-OS(O)H$, $-OSH$, $-SC(O)H$, $-S(O)C(O)OH$, $-SO_2C(O)OH$, $-NHSH$, $-NHS(O)H$, $-NHSO_2H$, $-C(O)SH$, $-C(O)S(O)H$, $-C(O)S(O_2)H$, $-C(S)H$, $-C(S)OH$, $-C(SO)OH$, $-C(SO_2)OH$, $-NHC(S)H$, $-OC(S)H$, $-OC(S)OH$, $-OC(SO_2)H$, $-S(O_2)NH_2$, $-S(O)NH_2$, $-SNH_2$, $-NHCS(O_2)H$, $-NHC(SO)H$, $-NHC(S)H$, and $-SH$ groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, $=O$, $-NO_2$, $-CN$, $-(CH_2)_z-CN$ where z is a whole integer from 0 to 4, $-OR_c$, $-NR_cOR_c$, $-NR_cR_c$, $-C(O)NR_c$, $-C(O)OR_c$, $-C(O)R_c$, $-NR_cC(O)NR_cR_c$, $-NR_cC(O)R_c$, $-OC(O)OR_c$, $-OC(O)NR_cR_c$, $-SR_c$, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted

cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

Provided herein are compositions and methods for treating a disease by administering an effective amount of kinase modulating compound having the structure:

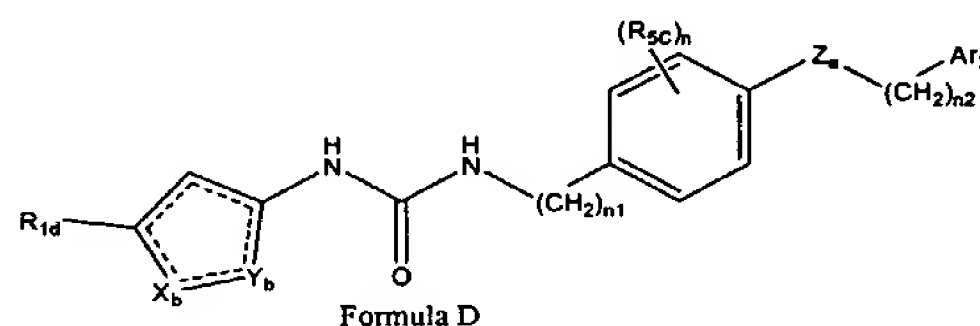


wherein:

- (a) R_{1C} is unsubstituted C_1 - C_5 alkyl or unsubstituted C_3 - C_6 cycloalkyl;
- (b) n is 0, 1 or 2; and
- (c) Each R_{5C} is a suitable substituent independently selected from the group consisting of halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-(CH_2)_zCN$ where z is a whole integer from 0 to 4, NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH₂, -NHC(NH)NH₂, -C(S)NH₂, -NHC(S)NH₂, -NHC(O)NH₂, -S(O₂)H, -S(O)H, -NH₂, -C(O)NH₂, -OC(O)NH₂, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O₂)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO₂C(O)OH, -NHSH, -NHS(O)H, -NH₂SO₂H, -C(O)SH, -C(O)S(O)H, -C(O)S(O₂)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO₂)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO₂)H, -S(O₂)NH₂, -S(O)NH₂, -SNH₂, -NHCS(O₂)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, -NO₂, -CN, $-(CH_2)_z-CN$ where z 0, 1, 2, 3, or 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -NR_cC(O)NR_cR_c, -NR_cC(O)R_c, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl,

or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

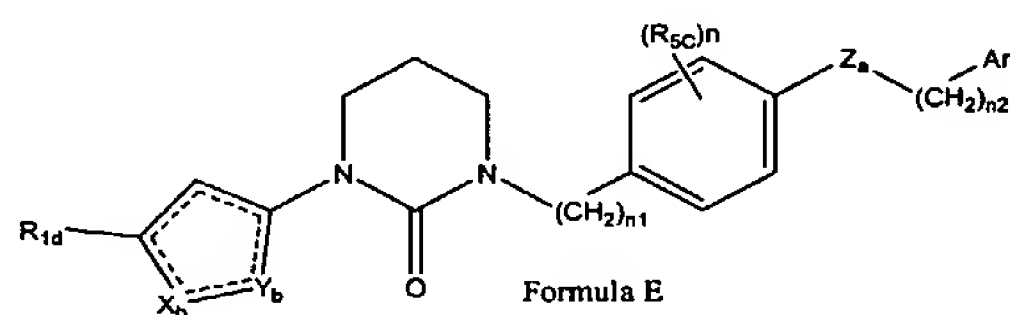
Provided herein are compositions and methods for treating a disease by administering an effective amount of kinase modulating compound having the structure:



wherein:

- (a) R_{1d} is unsubstituted C_1 - C_5 alkyl or unsubstituted C_3 - C_5 cycloalkyl;
- (b) n is 0, 1 or 2;
- (c) n_1 is 0, 1 or 2; and wherein n_2 is 0, 1 or 2; wherein n_1 and n_2 are not both 0.

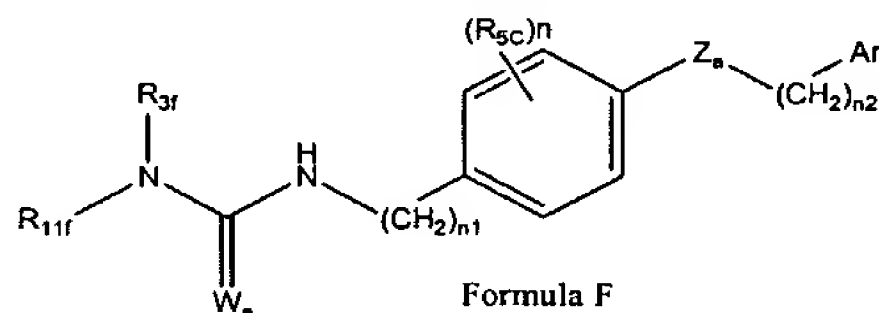
Provided herein are compositions and methods for treating a disease by administering an effective amount of a kinase modulating compound having the structure:



wherein:

- (a) n is 0, 1 or 2;

Provided herein are compositions and methods for treating a disease by administering an effective amount of a kinase modulating compound having the structure:

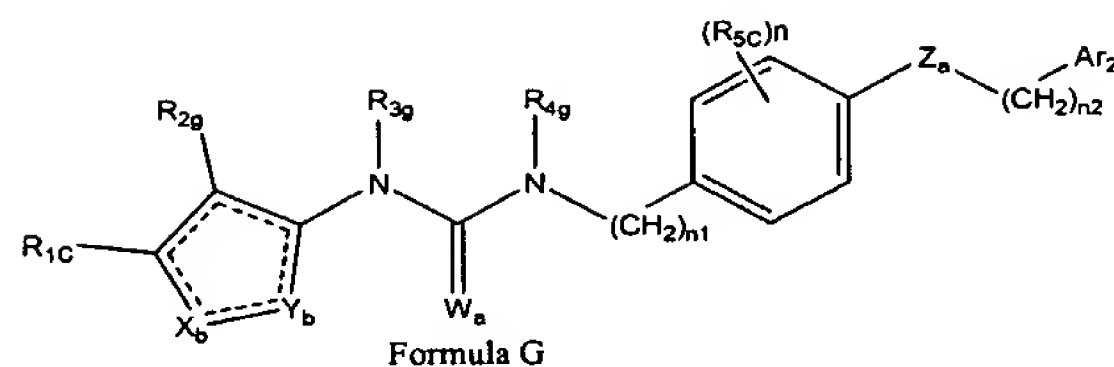


wherein:

- (a) R_{3f} and R_{11f} cyclize to form a heteroaryl or heterocycloalkyl group substituted or unsubstituted with one, two or three suitable substituents selected from the group

consisting of halogen, =O; =S; -CN; -NO₂, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of: halogens; =O; =S; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer from 0 to 4, =NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH₂, -NHC(NH)NH₂, -C(S)NH₂, -NHC(S)NH₂, -NHC(O)NH₂, -S(O₂)H, -S(O)H, -NH₂, -C(O)NH₂, -OC(O)NH₂, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O₂)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO₂C(O)OH, -NHSH, -NHS(O)H, -NH₂SO₂H, -C(O)SH, -C(O)S(O)H, -C(O)S(O₂)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO₂)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO₂)H, -S(O₂)NH₂, -S(O)NH₂, -SNH₂, -NHCS(O₂)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, -NO₂, -CN, -(CH₂)_z-CN where z is a whole integer from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -NR_cC(O)NR_cR_c, -NR_cC(O)R_c, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



wherein:

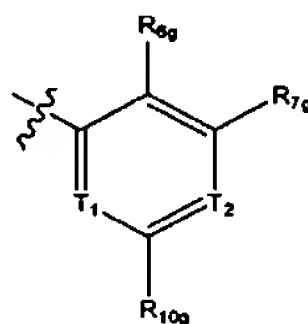
(a) R_{2g} , R_{3g} and R_{4g} are each independently selected from hydrogen, unsubstituted alkyl, unsubstituted aryl, and unsubstituted heteroaryl;

(b) n is 0, 1 or 2;

(c) n_1 is 0, 1 or 2;

(d) n_2 is 0, 1 or 2;

(e) Ar_2 is:



wherein:

(i) R_{6g} and R_{7g} cyclize to form a 5- or 6-membered aryl, heteroaryl, heterocycloalkyl or cycloalkyl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of: halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer from 0 to 4, NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH₂, -NHC(NH)NH₂, -C(S)NH₂, -NHC(S)NH₂, -NHC(O)NH₂, -S(O₂)H, -S(O)H, -NH₂, -C(O)NH₂, -OC(O)NH₂, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O₂)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO₂C(O)OH, -NHSH, NHS(O)H, -NHSO₂H, -C(O)SH, -C(O)S(O)H, -C(O)S(O₂)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO₂)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO₂)H, -S(O₂)NH₂, -S(O)NH₂, -SNH₂, -NHCS(O₂)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, -NO₂, -CN, -(CH₂)_z-CN where z is a whole integer from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -NR_cC(O)NR_cR_c,

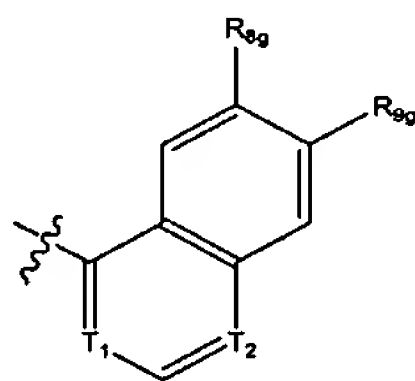
-NR_cC(O)R_c, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

(ii) R_{10g} is a suitable substituent selected from hydrogen; halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer from 0 to 4, NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH₂, -NHC(NH)NH₂, -C(S)NH₂, -NHC(S)NH₂, -NHC(O)NH₂, -S(O₂)H, -S(O)H, -NH₂, -C(O)NH₂, -OC(O)NH₂, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O₂)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO₂C(O)OH, -NHSH, NHS(O)H, -NH₂SO₂H, -C(O)SH, -C(O)S(O)H, -C(O)S(O₂)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO₂)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO₂)H, -S(O₂)NH₂, -S(O)NH₂, -SNH₂, -NHCS(O₂)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, =O, -NO₂, -CN, -(CH₂)_z-CN where z is a whole integer from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -NR_cC(O)NR_cR_c, -NR_cC(O)R_c, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group; and

(iii) T_1 and T_2 are each independently selected from CR_w and N, where R_w is a suitable substituent selected from hydrogen; halogens; -CN; and -NO₂; and unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group;

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

Compositions and methods of Formulas A-G are provided wherein X_b is O and Y_b is N and/or X_b is N and Y_b is O; and/or R_{2a} , R_{2g} , R_{3a} , R_{3g} , R_{4a} and R_{4g} are each hydrogen; and/or R_{1b} , R_{1c} , and R_{1d} are each an unsubstituted or substituted t-butyl and R_{2b} and R_{2g} are hydrogen; and/or W_a is O; and/or Z_a is C(O)NH or NHC(O); and/or n is 0. In various embodiments, T_1 is N and T_2 is N or T_1 is N and T_2 is CH. In other embodiments, Ar_2 is:



wherein:

(i) R_{8g} and R_{9g} are suitable substituents each independently selected from the group consisting of hydrogen; halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer from 0 to 4, -NH, -NHOH, -OH, -C(O)H, -OC(O)H, -C(O)OH, -OC(O)OH, -OC(O)OC(O)H, -OOH, -C(NH)NH₂, -NHC(NH)NH₂, -C(S)NH₂, -NHC(S)NH₂, -NHC(O)NH₂, -S(O₂)H, -S(O)H, -NH₂, -C(O)NH₂, -OC(O)NH₂, -NHC(O)H, -NHC(O)OH, -C(O)NHC(O)H, -OS(O₂)H, -OS(O)H, -OSH, -SC(O)H, -S(O)C(O)OH, -SO₂C(O)OH, -NHSH, -NHS(O)H, -NH₂SO₂H, -C(O)SH, -C(O)S(O)H, -C(O)S(O₂)H, -C(S)H, -C(S)OH, -C(SO)OH, -C(SO₂)OH, -NHC(S)H, -OC(S)H, -OC(S)OH, -OC(SO₂)H, -S(O₂)NH₂, -S(O)NH₂, -SNH₂, -NHCS(O₂)H, -NHC(SO)H, -NHC(S)H, and -SH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens,

=O, -NO₂, -CN, -(CH₂)_z-CN where z is a whole integer from 0 to 4, -OR_c, -NR_cOR_c, -NR_cR_c, -C(O)NR_c, -C(O)OR_c, -C(O)R_c, -NR_cC(O)NR_cR_c, -NR_cC(O)R_c, -OC(O)OR_c, -OC(O)NR_cR_c, -SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group; and

(ii) T₁ is N and T₂ is CH or N.

Compositions and methods of Formulas A-G are provided herein wherein R_{8g} and R_{9g} are each independently selected from the group consisting of hydrogen; halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer from 0 to 4, -OH, -C(O)H, -OC(O)H, -C(O)OH, -NH₂, -C(O)NH₂, -NHC(O), -OC(O)NH₂, -NHC(O)H, -NHC(O)OH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group.

Compositions and methods of Formulas A-G are provided herein wherein each R_{5c} is a suitable substituent independently selected from the group consisting of halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer from 0 to 4, -OH, -C(O)H, -OC(O)H, -C(O)OH, -NH₂, -C(O)NH₂, -NHC(O), -OC(O)NH₂, -NHC(O)H, -NHC(O)OH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted

cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group.

Compositions and methods of Formula A are provided herein wherein Ar₃ is a 5-membered aryl, heteroaryl, heterocycloalkyl or cycloalkyl group unsubstituted or substituted with one, two or three suitable substituents. In some embodiments, Ar₃ is a 5- or 6-membered aryl or heteroaryl group unsubstituted or substituted with one, two or three suitable substituents.

Compositions and methods of Formula A-G are provided herein wherein n₃ is 0 or 1, and/or wherein n₁ is 0, 1 or 2, and/or n₂ is 0, 1 or 2. In some embodiments, R_{3a}/R_{3g} and R_{4a}/R_{4g} are each hydrogen. In other embodiments, R_{3a}/R_{3g} and R_{4a}/R_{4g} are not both substituted.

Compositions and methods of Formula A are provided herein wherein Ar₃ is a substituted or unsubstituted 5-membered heteroaryl group and R₂ is hydrogen. In some embodiments, Ar₁ is an unsubstituted or substituted 6-membered aryl group or an unsubstituted or substituted 6-membered heteroaryl group. In other embodiments, W_a is O.

Compositions and methods of Formulas A-G wherein Z_a is not carbon are described herein. In some embodiments, Z_a is selected from S, O, N, NR_{c2}, C(O)NR_{c2}, and NR_{c2}C(O), wherein R_{c2} is hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl group. In other embodiments, Z_a is C(O)NH, NHC(O), or NH.

Compositions and methods of Formulas A-G wherein W_a is S, O, or NH are described herein.

Compositions and methods of Formulas A-G are described herein wherein Ar₁ is an aryl or heteroaryl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer from 0 to 4, -OH, -C(O)H, -OC(O)H, -C(O)OH, -NH₂, -C(O)NH₂, -NHC(O), -OC(O)NH₂, -NHC(O)H, -NHC(O)OH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, unsubstituted alkyl, unsubstituted alkenyl,

unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl.

Compositions and methods of Formulas A-G are described herein wherein Ar₂ is an aryl, heteroaryl, heterocycloalkyl or cycloalkyl group unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens; -CN; and -NO₂; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, -(CH₂)_zCN where z is a whole integer from 0 to 4, -OH, -C(O)H, -OC(O)H, -C(O)OH, -NH₂, -C(O)NH₂, -NHC(O), -OC(O)NH₂, -NHC(O)H, -NHC(O)OH groups unsubstituted or substituted with one, two or three suitable substituents independently selected from the group consisting of halogens, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl. In some embodiments, Ar₂ is an unsubstituted or substituted pyridinyl. In other embodiments, Ar₂ is an unsubstituted or substituted quinazolinyl.

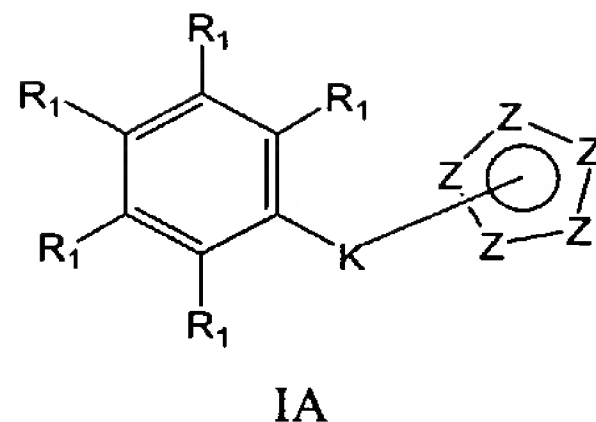
Compositions and methods of Formulas A-G are provided herein wherein X_b and Y_b are each independently selected from O, N, and NR_{c1} wherein R_{c1} is unsubstituted alkyl or unsubstituted aryl. In some embodiments, X_b is N and Y_b is NR_{c1}. In other embodiments, X_b is O and Y_b is N. In other embodiments, X_b is O and Y_b is N, or X_b is N and Y_b is O.

Compositions and methods of Formulas A-G are provided herein wherein R₁ is unsubstituted t-butyl or unsubstituted cyclopropyl.

Compositions and methods are provided herein wherein R_{5c} is independently selected from the group consisting of halogens, -CN, -NO₂, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted heteroalkyl, unsubstituted haloalkyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl group.

Compositions and methods of Formulas A-G are provided herein wherein R_{10g} is hydrogen or lower alkyl.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



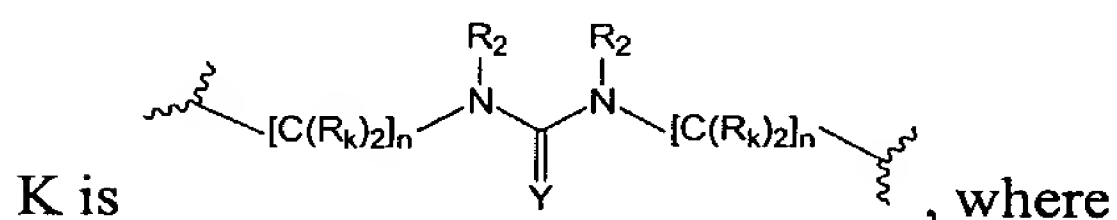
wherein:

each Z is independently C, CR₃, N, NR₃, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

5 where R₃ is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

each R₁ is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR_c, -OC(O)R_c, -NO₂, -N(R_c)₂, -SR_c, S(O)_jR_c where j is 1 or 2, -NR_cC(O)R_c, -C(O)N(R_c)₂, -C(O)₂R_c, or -C(O)R_c; or two adjacent R₁'s, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

15 each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.



Y is O or S;

20 each R_k is independently H, halogen, substituted or unsubstituted alkyl, -OR₂, substituted or unsubstituted alkoxy, -OC(O)R₂, -NO₂, -N(R₂)₂,

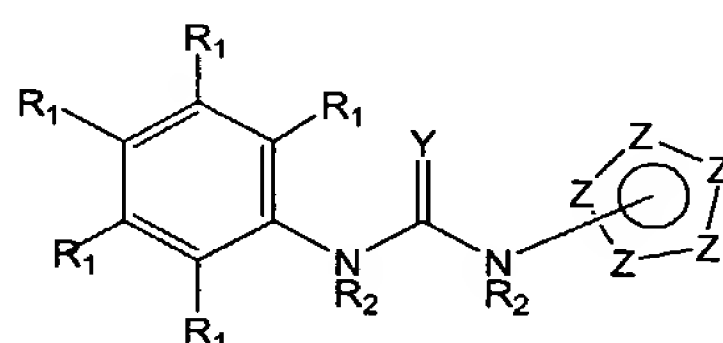
-SR₂, -C(O)R₂, -C(O)₂R₂, -C(O)N(R₂)₂, or -N(R₂)C(O)R₂;

25 each R₂ is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted

heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and
each n is independently 0, 1, 2, 3 or 4;

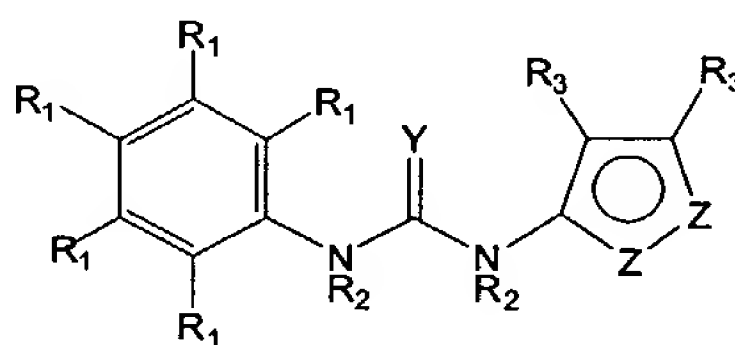
or an active metabolite, or a pharmaceutically acceptable prodrug, isomer,
pharmaceutically acceptable salt or solvate thereof.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



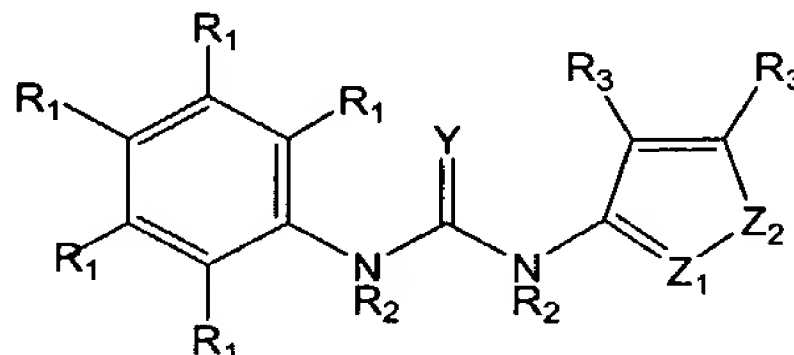
(I).

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(II).

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



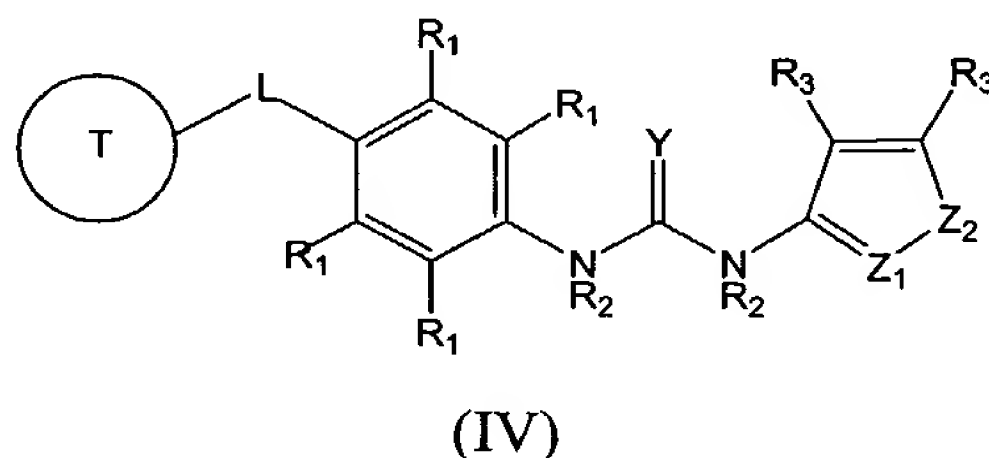
(III)

wherein:

Z_1 is CR_3 or N; and

Z_2 is O or S.

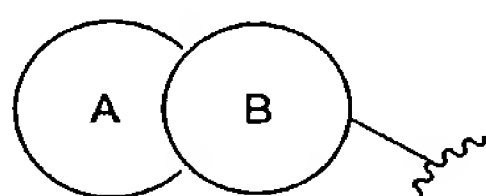
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



wherein:

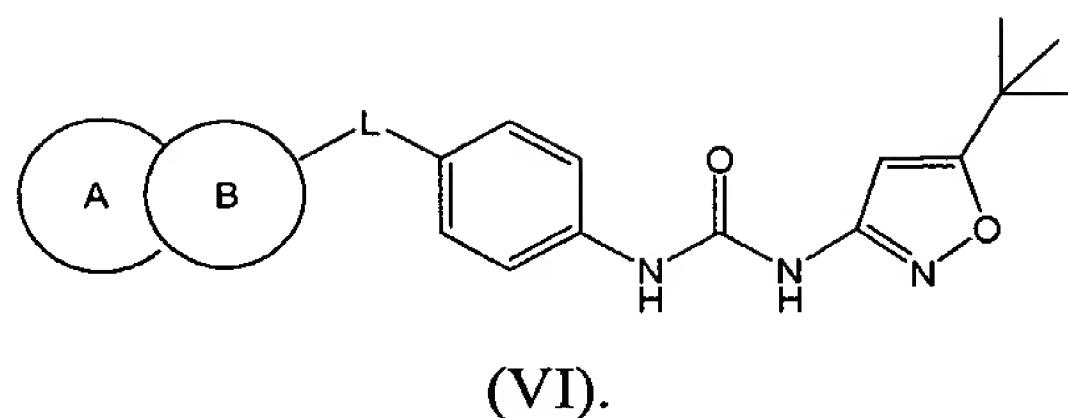
L is a linker selected from the group consisting of a covalent bond, -(substituted or unsubstituted alkylene)-, -(substituted or unsubstituted alkenylene)-, -O-, -O(substituted or unsubstituted alkylene)-, -C(O)-, -C(O)(substituted or unsubstituted alkylene)-, -C(O)(substituted or unsubstituted alkenylene)-, -NH-, -NH(substituted or unsubstituted alkylene)-, -NH(substituted or unsubstituted alkenylene)-, -C(O)NH-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -S-, -S(substituted or unsubstituted alkylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

T is a mono-, bi-, or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.



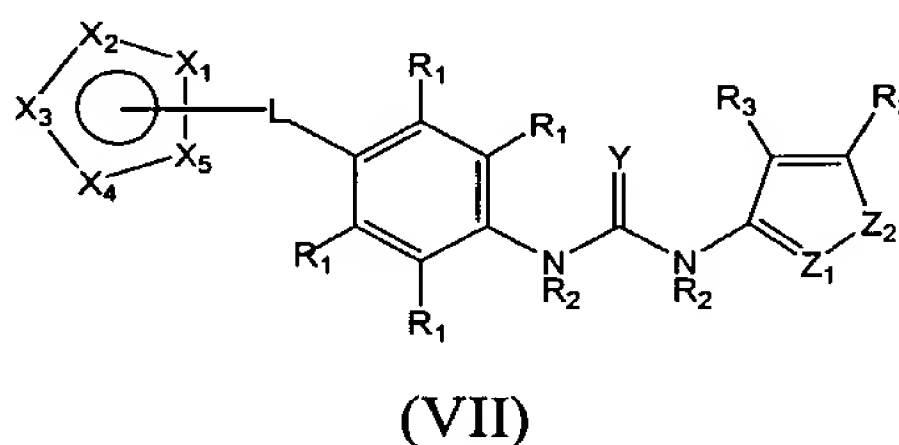
In some embodiments, T is wherein A is a substituted or unsubstituted five or six-membered aryl, heterocyclyl or heteroaryl; and B is a substituted or unsubstituted five or six-membered arylene, heterocyclene or heteroarylene, wherein A and B together form a fused two-ring moiety.

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



In some embodiments, L is $-\text{C}(\text{O})\text{NH}-$. In other embodiments, B is substituted or unsubstituted phenylene, pyridinylene, pyrimidinylene, pyridazinylene, thiophenylene, imidazolylene, or pyrrolylene. In still other embodiments, L is $-\text{NH}-$. In yet other
 5 embodiments, B is substituted or unsubstituted phenylene, pyridinylene, pyrimidinylene, pyridazinylene, thiophenylene, or imidazolylene.

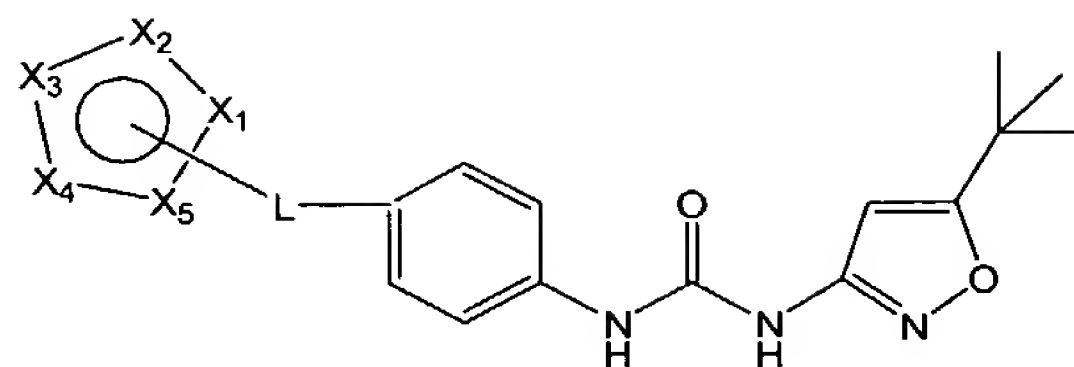
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating
 10 compound having the following structure:



wherein:

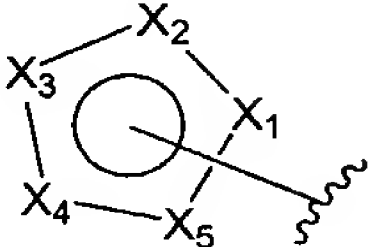
each of $\text{X}_1\text{-X}_5$ is independently C, CR, N, NR, S, or O, wherein no more than three of
 15 $\text{X}_1\text{-X}_5$ is a heteroatom, and no two adjacent ring atoms are O or S; where
 each R is independently H, halogen, substituted or unsubstituted alkyl, $-\text{OH}$,
 substituted or unsubstituted alkoxy, $-\text{OC}(\text{O})\text{R}_d$, $-\text{NO}_2$, $-\text{N}(\text{R}_d)_2$, $-\text{SR}_d$, $-\text{S}(\text{O})_j\text{R}_d$
 where j is 1 or 2, $-\text{NR}_d$ $\text{C}(\text{O})\text{R}_d$, $-\text{C}(\text{O})_2\text{R}_d$, $-\text{C}(\text{O})\text{N}(\text{R}_d)_2$, or $-\text{C}(\text{O})\text{R}_d$, or two
 20 adjacent R_d 's are taken together to form a substituted or unsubstituted aryl or
 heteroaryl,
 where each R_d is independently H, substituted or unsubstituted alkyl,
 substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 aryl, or substituted or unsubstituted heteroaryl.

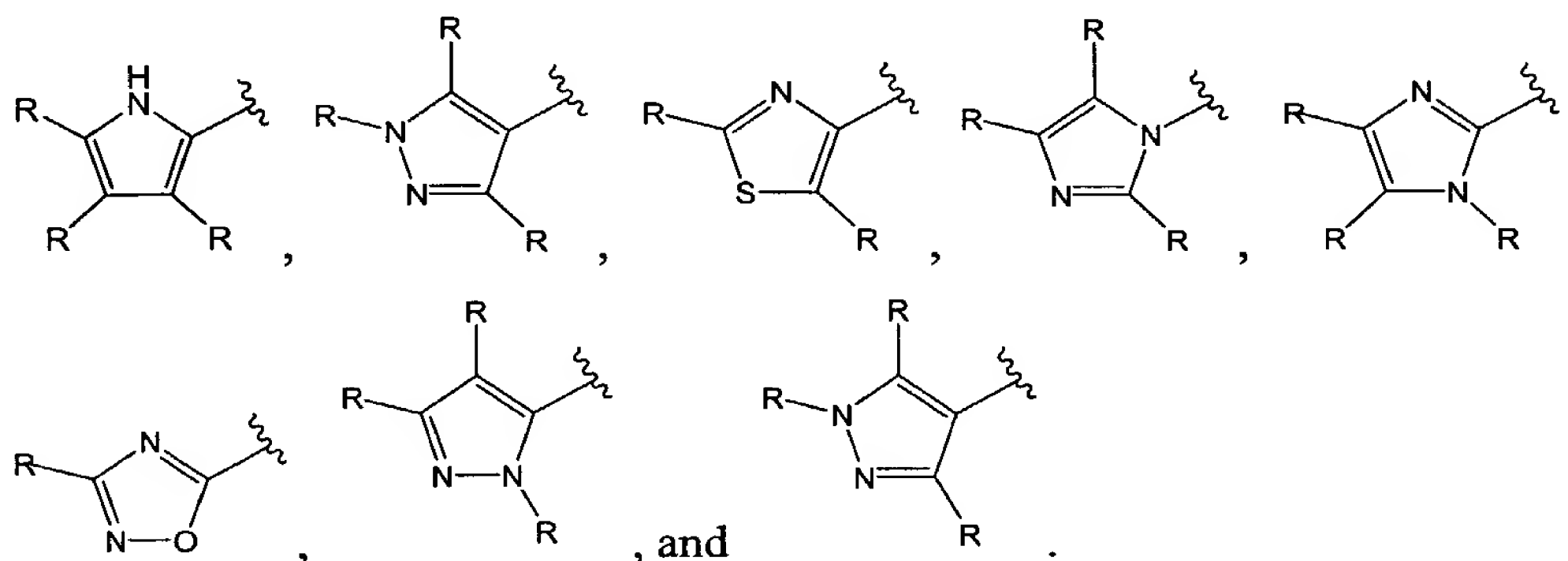
Provided herein are compositions and methods for treating a disease comprising
 25 administering to a subject in need thereof an effective amount of a kinase modulating
 compound having the following structure:



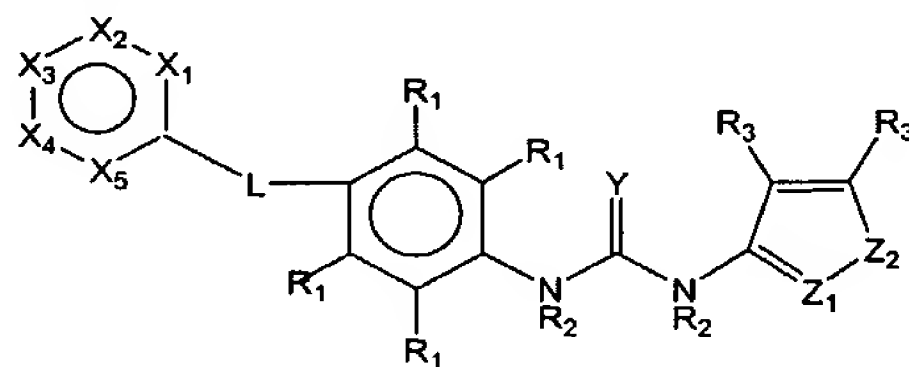
(VIII).

In some embodiments, L is a covalent bond, -C(O)NH-, -OCH₂-, or -OCH₂CH₂-. In other

embodiments,  is selected from the group consisting of:

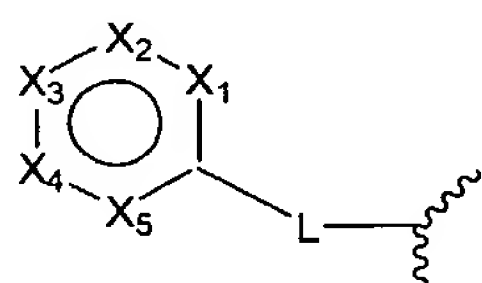


Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(IX)

wherein:



is selected from the group consisting of:

- (a) L is selected from the group consisting of -O(substituted or unsubstituted alkylene)-, and -C(O)(substituted or unsubstituted alkenylene)-; and

each of X_1 - X_5 is independently CR, N-O, or N, wherein no more than two of X_1 - X_5 is N, where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -NR_dC(O) R_d , or -C(O) R_d ,

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(b) L is -NH-;

each of X_1 , X_2 , X_4 , and X_5 is independently CR, N-O, or N; and X_3 is independently CR₅ or N, wherein no more than two of X_1 - X_5 is N, where R_5 is selected from the group consisting of H, halogen, substituted or unsubstituted alkyl, substituted alkoxy, -C(O) R_d , -OC(O) R_d , -NO₂, -N(R_d)₂, and -SR_d, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(c) L is -NH-;

each of X_1 , X_3 , and X_5 is independently CR, N-O, or N; and each of X_2 and X_4 is independently CR₆ or N, wherein no more than two of X_1 - X_5 is N; where

R_6 is selected from the group consisting of H, halogen, unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -C(O) R_d , -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, and alkyl substituted with alkoxy, halogen, aryl, heteroaryl, amine, -C(O) R_d , -OC(O) R_d , -NO₂, -N(R_d)₂, and -SR_d, and

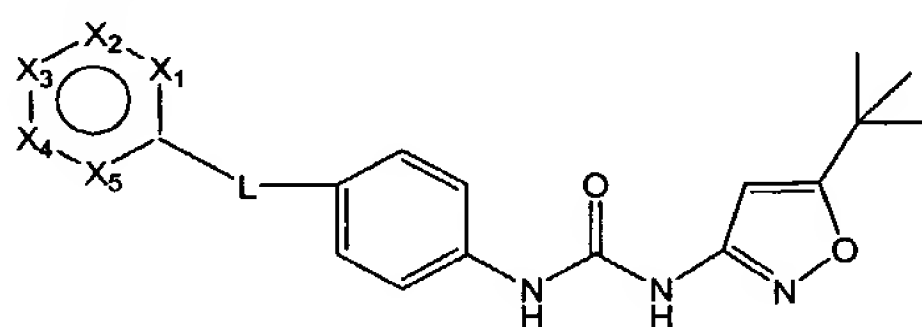
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(d) L is -C(O)NH-;

each of X_1 , X_2 , X_4 , and X_5 is independently CR, N-O, or N; and
 X_3 is independently CR₇ or N, wherein no more than two of X_1 - X_5 is N, and
 when X_3 is N, at least one of X_1 , X_2 , X_3 , or X_5 is not CH, where

R_7 is selected from the group consisting of H, halogen, substituted or
 unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy,
 -C(O) R_d , -OC(O) R_d , -NO₂, -N(R_d)₂, and -SR_d, and
 each R_d is independently H, substituted or unsubstituted alkyl,
 substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 aryl, or substituted or unsubstituted heteroaryl.

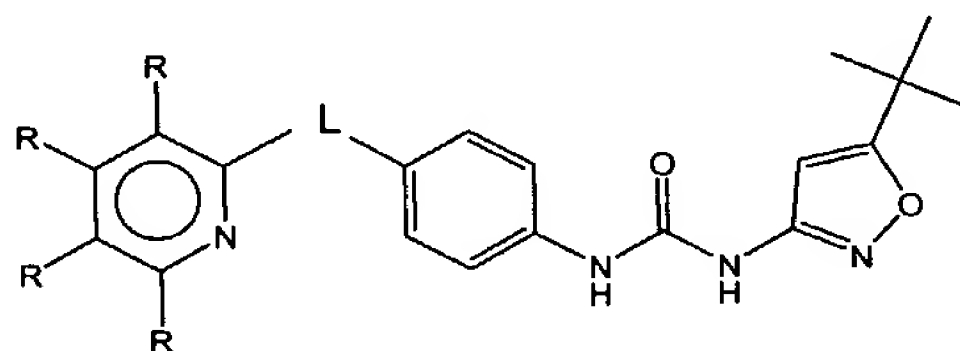
Provided herein are compositions and methods for treating a disease comprising
 administering to a subject in need thereof an effective amount of a kinase modulating
 compound having the following structure:



(X).

In some embodiments, L is a linker selected from the group consisting of a covalent bond, -
 (substituted or unsubstituted alkylene), -NHC(O)-, -C(O)NH(substituted or unsubstituted
 alkylene), -NHC(O)(substituted or unsubstituted alkylene), -C(O)NH(substituted or
 unsubstituted alkenylene), -NHC(O)(substituted or unsubstituted alkenylene)-, and -
 O(substituted or unsubstituted alkylene)-.

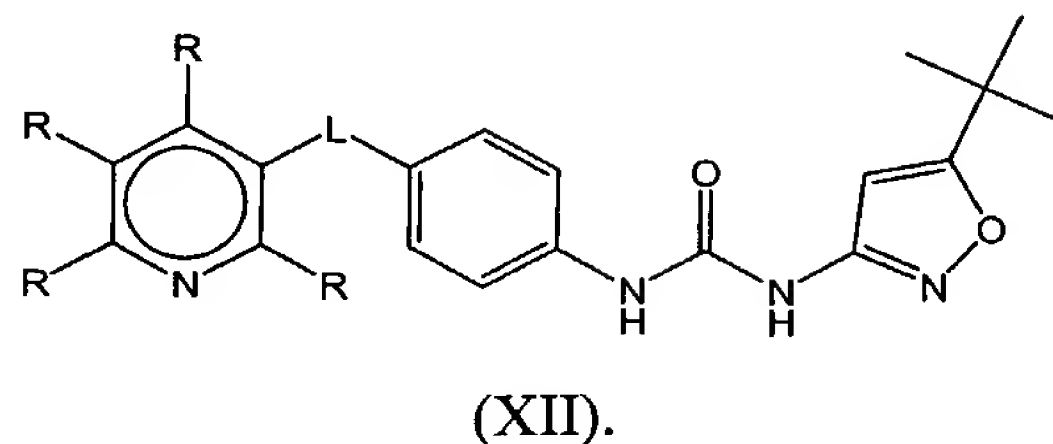
Provided herein are compositions and methods for treating a disease comprising
 administering to a subject in need thereof an effective amount of a kinase modulating
 compound having the following structure:



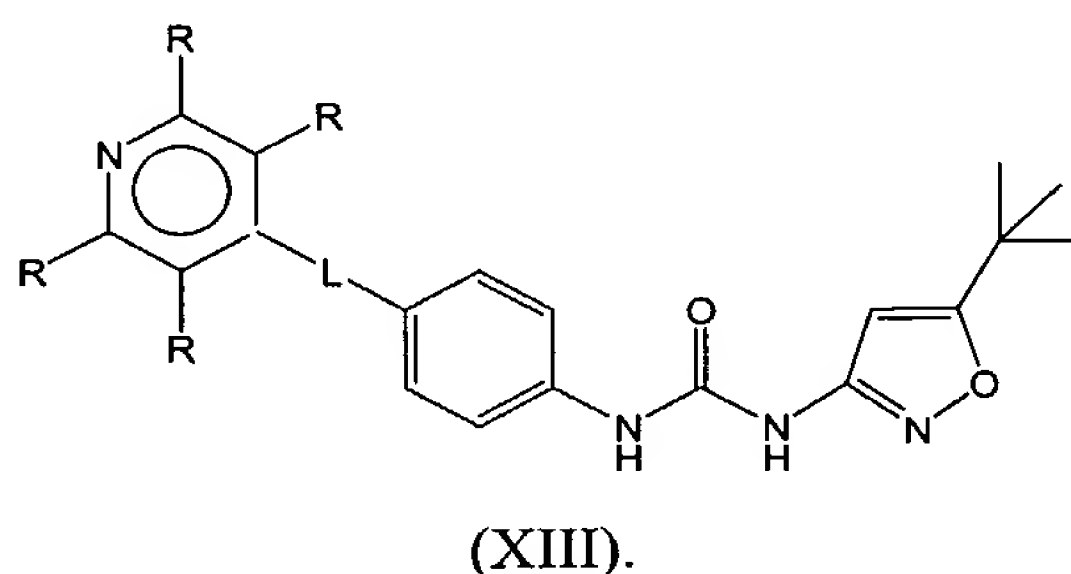
(XI).

Provided herein are compositions and methods for treating a disease comprising
 administering to a subject in need thereof an effective amount of a kinase modulating

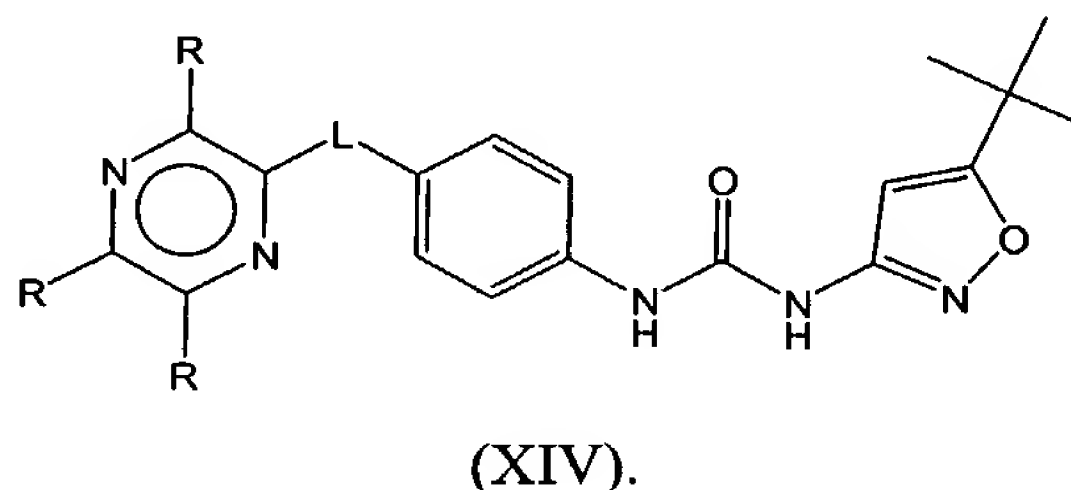
compound having the following structure:



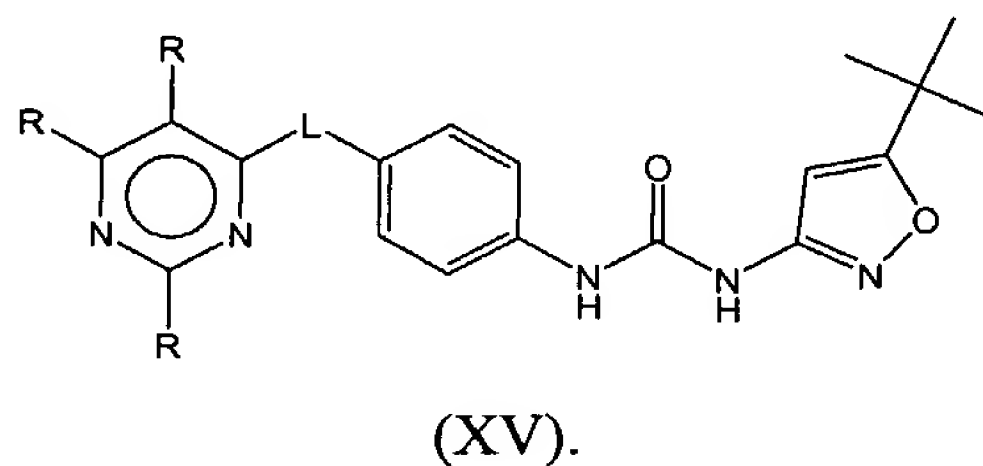
5 Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



10 Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:

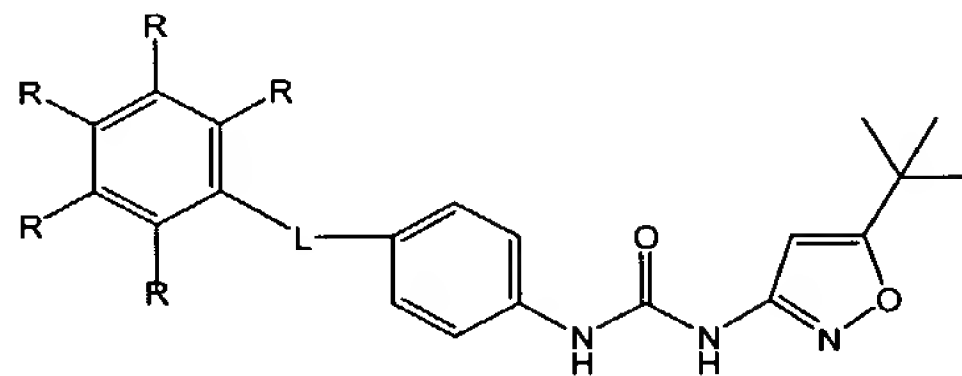


15 Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



Provided herein are compositions and methods for treating a disease comprising

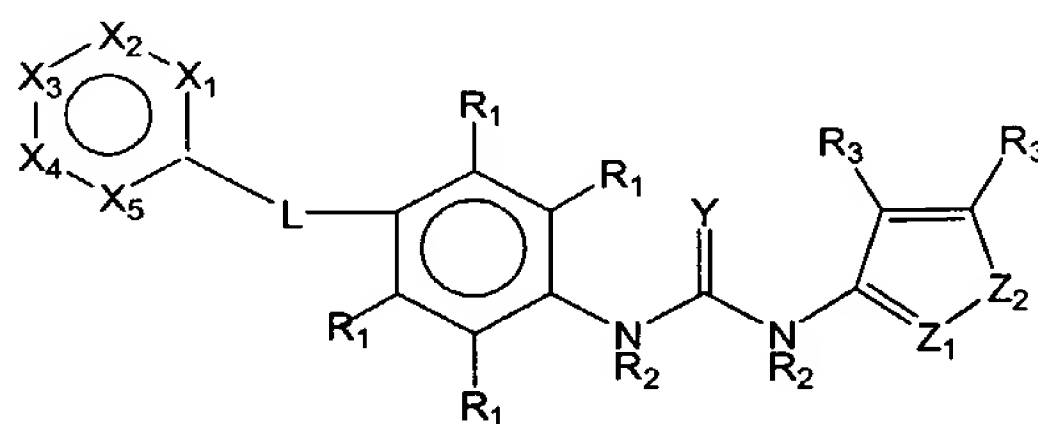
administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XVI).

5 In some embodiments, L is a linker selected from the group consisting of -NHC(O)-, -OCH₂-, -OCH₂CH₂-, -NHC(O)CH₂SCH₂C(O)NH-, -CHCHC(O)NH-, -CHCHCH₂O-, -CH₂CH₂-, and -CH₂CH₂C(O)NH-.

10 Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XVII)

wherein:

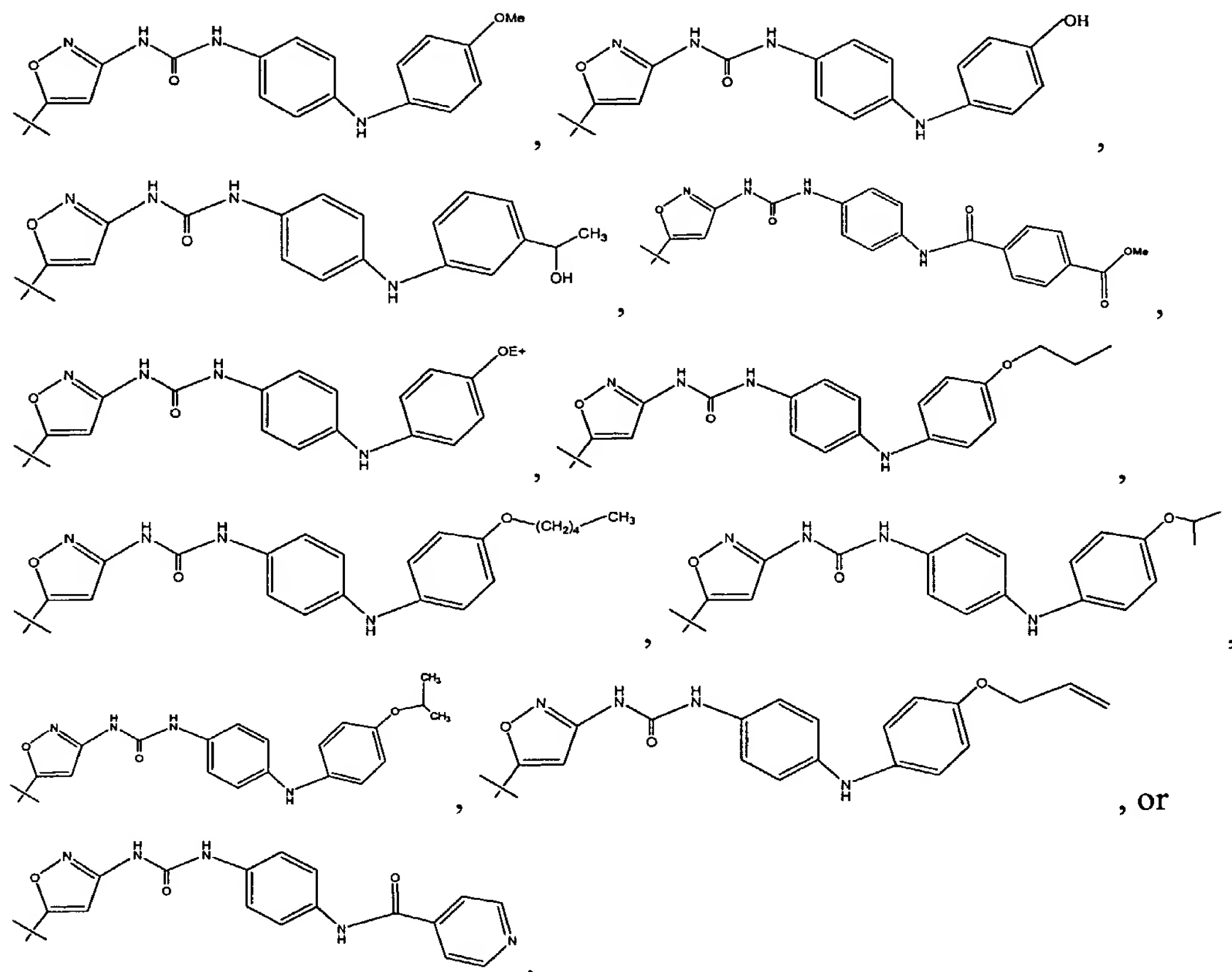
each of X₁-X₅ is independently C, CR, N-O, or, wherein no more than two of X₁-X₅ is N; where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OR_d, substituted or unsubstituted alkoxy, -OC(O)R_d, -NO₂, -N(R_d)₂, -SR_d, -S(O)_jR_d where j is 1 or 2, -NR_d C(O)R_d, -C(O)₂R_d, -C(O)N(R_d)₂ or -C(O)R_d; or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl

with a proviso that said compound is not:

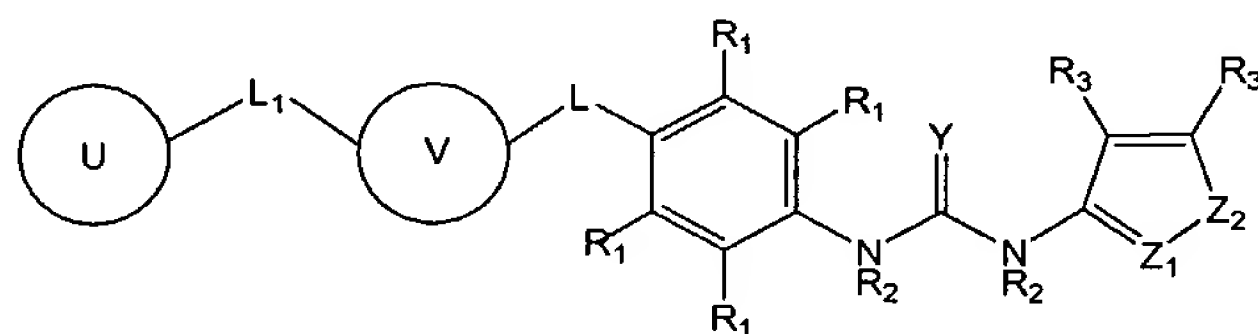
5



, or

Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:

10



(XVIII)

wherein:



is selected from the group consisting of:

- (a) each of L and L_1 is independently a linker selected from the group consisting of a covalent bond, $-O(\text{substituted or unsubstituted alkylene})-$, $-S-$, $-$

15

(substituted or unsubstituted alkylene)-, -C(O)-, and -N(substituted or unsubstituted alkylene)-;

U is a substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl;
and

5 V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene;

(b) L is a linker selected from the group consisting of a covalent bond,
-O(substituted or unsubstituted alkylene)-, -S-, -(substituted or
unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted
10 or unsubstituted alkylene)-;

L₁ is a linker selected from the group consisting of a covalent
bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or
unsubstituted alkylene)-, -O-, -NH-, -C(O)-, and -N(substituted or
unsubstituted alkylene)-;

15 U is selected from the group consisting of:

- (i) substituted or unsubstituted cycloalkyl;
- (ii) unsubstituted aryl;
- (iii) aryl substituted at any position with -Cl, -I, substituted or
unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -
20 OC(O)R₃, -NO₂, -N(R_g)₂, -SR_g, -C(O)R_h, where R_h is H, -OH, -
N(R_g)₂, or substituted or unsubstituted alkoxy, and where R_g is H or
substituted or unsubstituted alkyl; and
- (iv) substituted or unsubstituted heteroaryl, except pyridinyl; and

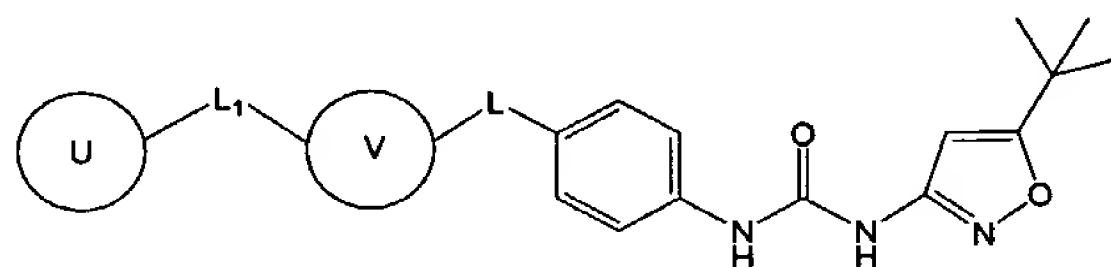
25 V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene; and

(c) L is a linker selected from the group consisting of a covalent
bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or
unsubstituted alkylene)-,
-O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted
30 alkylene)-;

L_1 is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted C_2 - C_5 alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

U is selected from the group consisting of substituted or unsubstituted cycloalkyl; substituted aryl; and substituted or unsubstituted heteroaryl; and V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

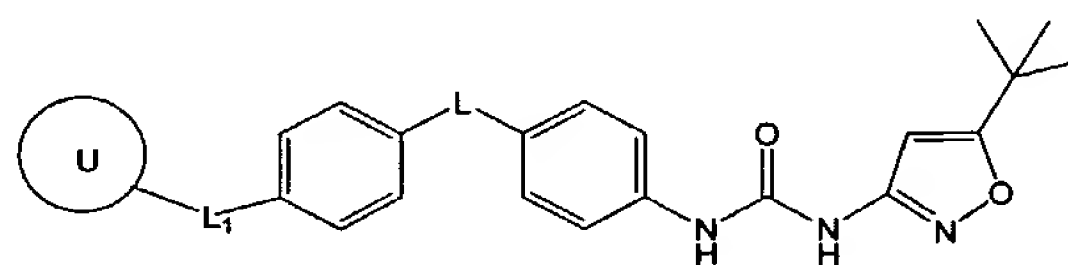
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XIX).

In some embodiments, L_1 is a bond; and L is a bond or -C(O)NH-. In other embodiments, U is substituted or unsubstituted phenyl, thiazolyl, or pyridinyl; and V is substituted or unsubstituted piperidinylene, thiazolylen, imidazolylene, or thiophenylene.

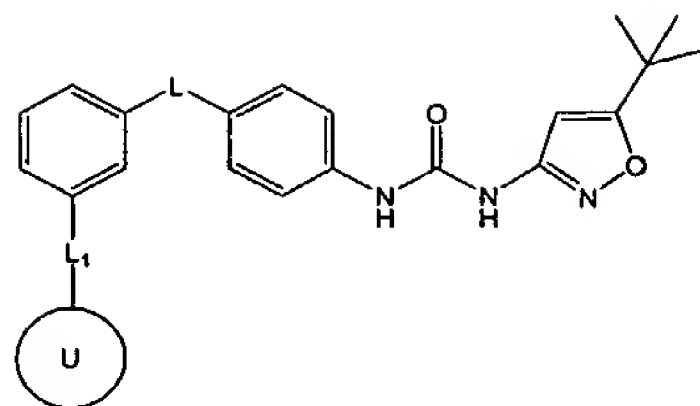
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XX).

In some embodiments, L_1 is a bond, -CH₂O-, -N(CH₃)-, or -O-; and L is -CH₂O- or -NHC(O)-. In other embodiments, U is substituted or unsubstituted phenyl, C_3 - C_6 cycloalkyl, pyrimidine, or pyridine.

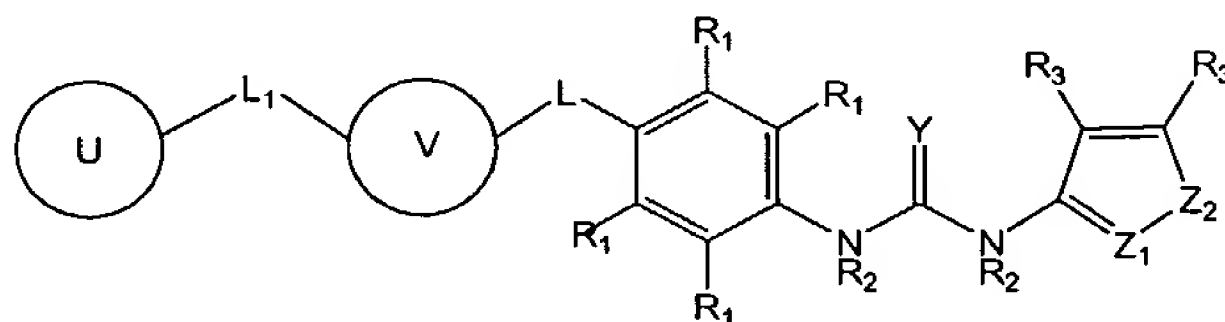
Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XXI).

In some embodiments, L_1 is a $-NH-$ or $-O-$; and L is $-NHC(O)-$. In other embodiments, U is substituted or unsubstituted pyrimidyl.

5 Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a kinase modulating compound having the following structure:



(XXII)

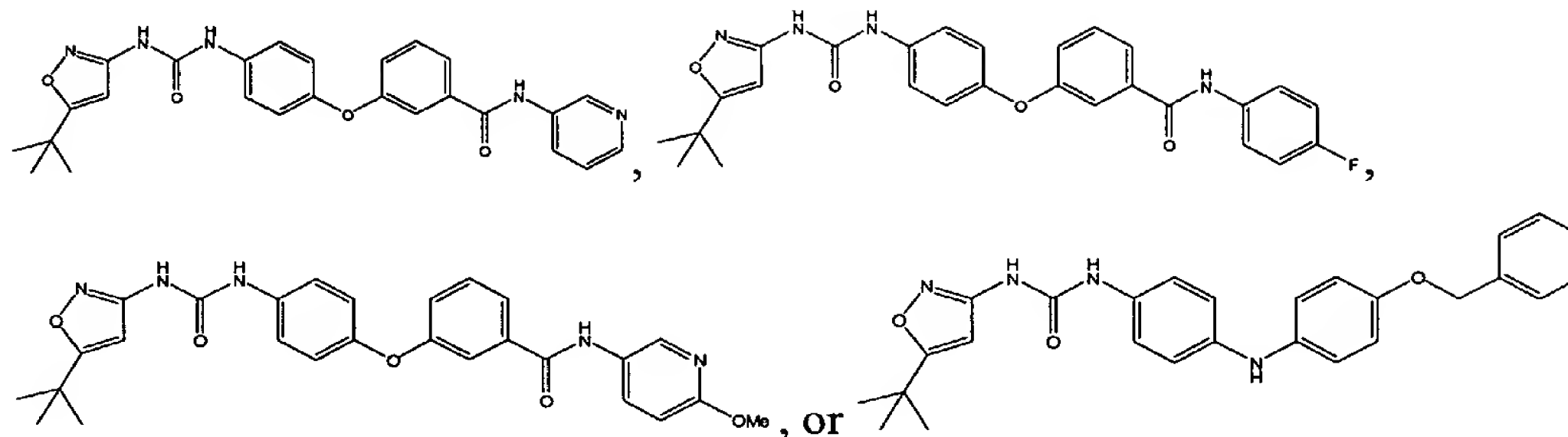
10 wherein:

L and L_1 is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-C(O)NH-$, $-C(O)-$, $-NH-$, $-O-$, $-S-$, $-O(\text{substituted or unsubstituted alkylene})-$, $-N(\text{substituted or unsubstituted alkylene})-$, $C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkenylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkenylene})-$, $-C(O)(\text{substituted or unsubstituted alkenylene})-$, and $-NHC(O)(\text{substituted or unsubstituted alkylene})S(\text{substituted or unsubstituted alkylene})C(O)NH-$;

U is a substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

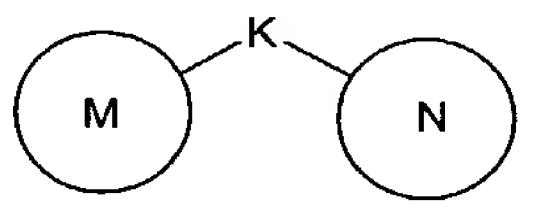
V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene;

25 with a proviso that said compound is not:



Exemplary FLT-3 Modulators

5 Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound corresponding to the following formula are provided herein:

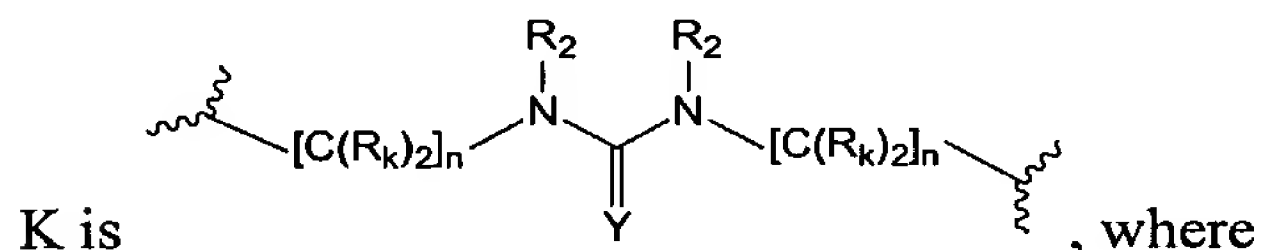


wherein:

M is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

10 N is a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

and



Y is O or S;

each R_k is independently H, halogen, substituted or unsubstituted alkyl,

15 -OH, substituted or unsubstituted alkoxy, -OC(O) R_2 , -NO₂, -N(R_2)₂, -SR₂, -C(O) R_2 , -C(O)₂ R_2 , -C(O)N(R_2)₂, or -N(R_2)C(O) R_2 ,

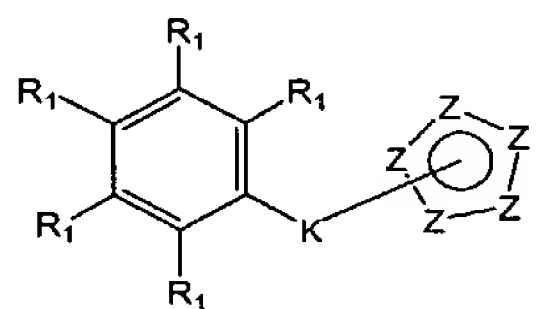
each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

20

each n is independently 0, 1, 2, 3 or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein:

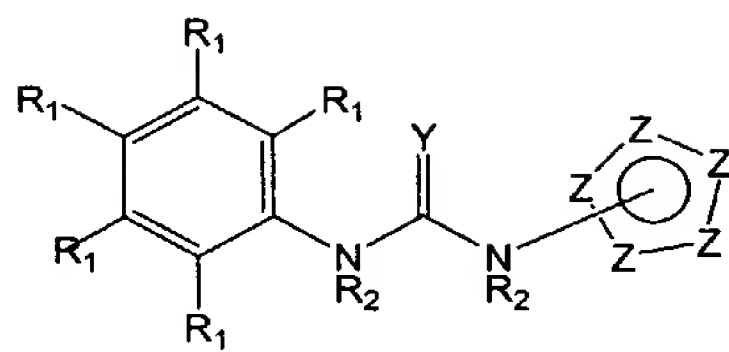
each Z is independently C, CR₃, N, NR₃, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

where R₃ is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

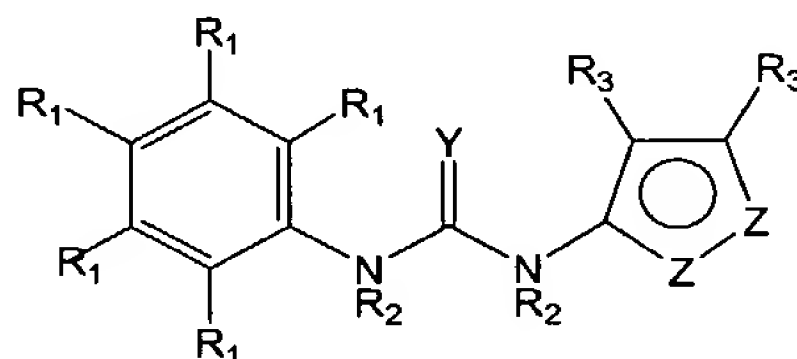
each R₁ is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR_c, -OH, -OC(O)R_c, -NO₂, -N(R_c)₂, -SR_c, S(O)_jR_c where j is 1 or 2, -NR_cC(O)R_c, -C(O)N(R_c)₂, C(O)₂R_c, or -C(O)R_c; or two adjacent R₁'s, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

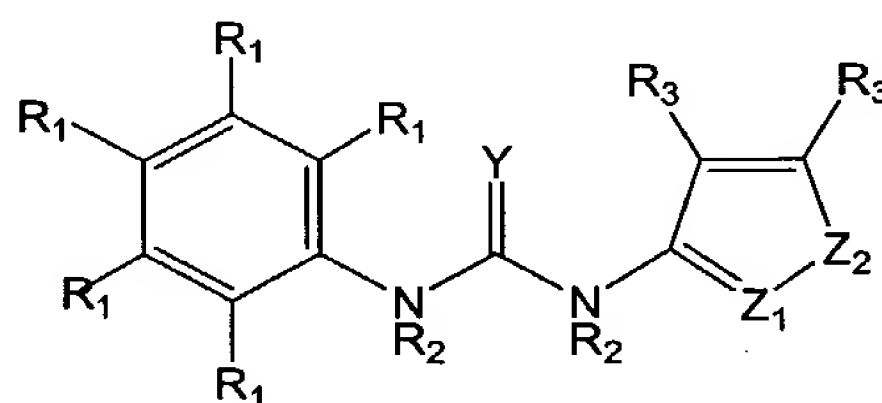


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



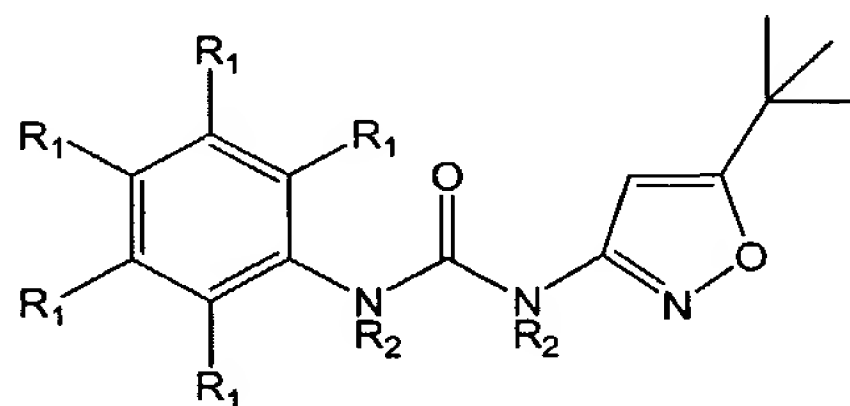
5

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



10 wherein Z_1 is CR_3 or N; and Z_2 is O or S.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

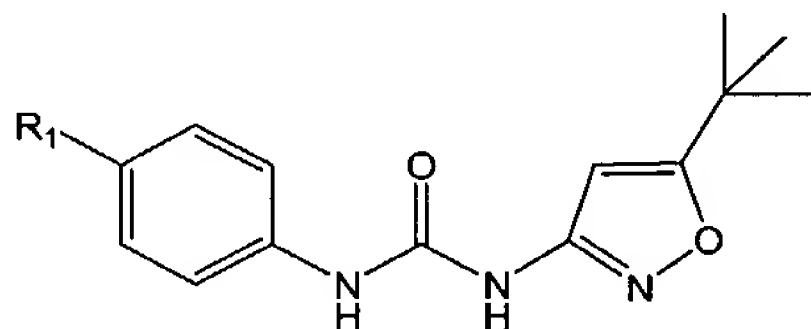


15 wherein:

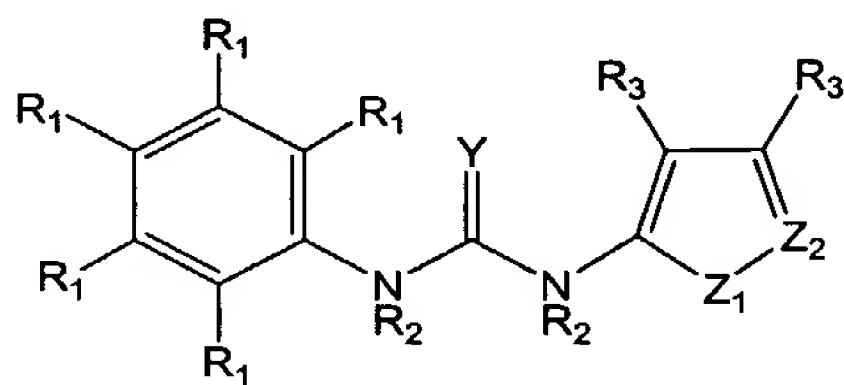
each R_1 is independently H, halogen, substituted or unsubstituted alkyl, -O(substituted or unsubstituted alkyl), -O(substituted or unsubstituted alkenyl), -NR_cC(O)O(substituted or unsubstituted alkyl), -NR_cC(O)(substituted or unsubstituted alkyl), -NR_cC(O)(substituted or unsubstituted alkenyl), -C(O)NR_c(substituted or unsubstituted alkyl), -C(O)NR_c(substituted or unsubstituted alkenyl), -NO₂, -S(=O)R_c, -SR_c, C(O)₂R_c, or -C(O)R_c; and

each R_2 is independently H or substituted or unsubstituted alkyl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

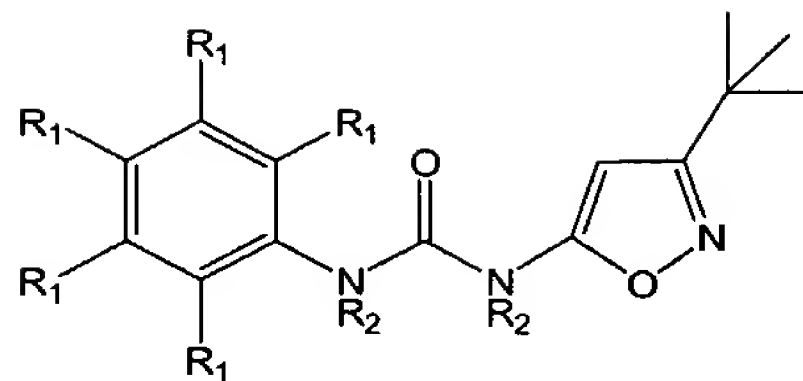


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein Z_1 is O or S; and Z_2 is CR₃ or N.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

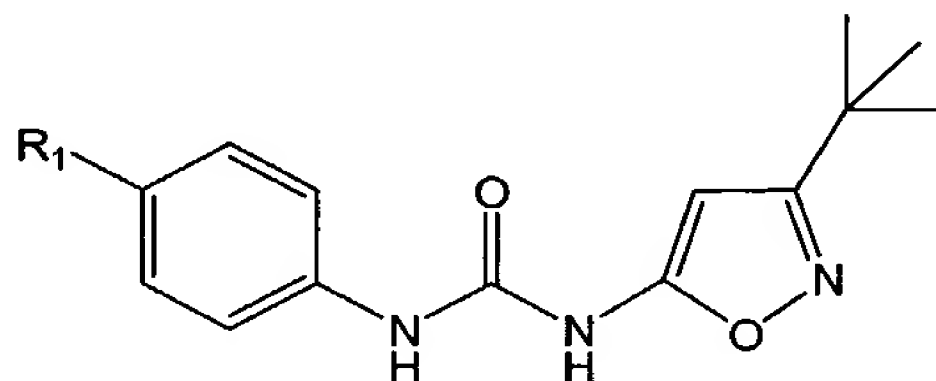


wherein:

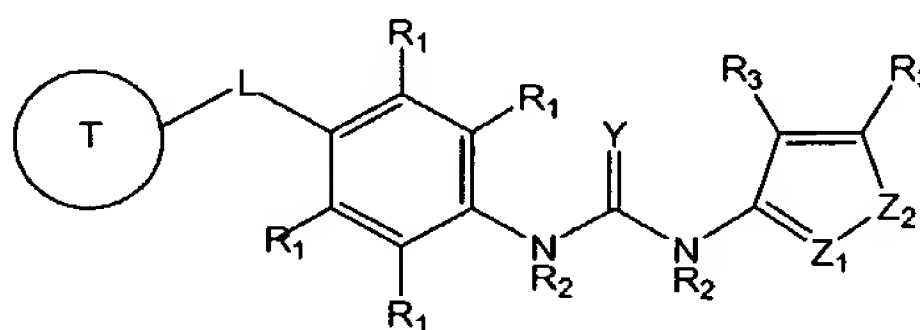
each R₁ is independently H, halogen, substituted or unsubstituted alkyl, -O(substituted or unsubstituted alkyl), -O(substituted or unsubstituted alkenyl), -NR_cC(O)O(substituted or unsubstituted alkyl), -NR_cC(O) (substituted or unsubstituted alkyl), -NR_cC(O)(substituted or unsubstituted alkenyl), -C(O)NR_c(substituted or unsubstituted alkyl), -C(O)NR_c(substituted or unsubstituted alkenyl), -NO₂, -S(=O)R_c, -SR_c, C(O)₂R_c, or -C(O)R_c; and

each R₂ is independently H or substituted or unsubstituted alkyl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



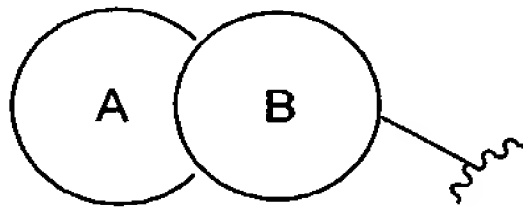
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



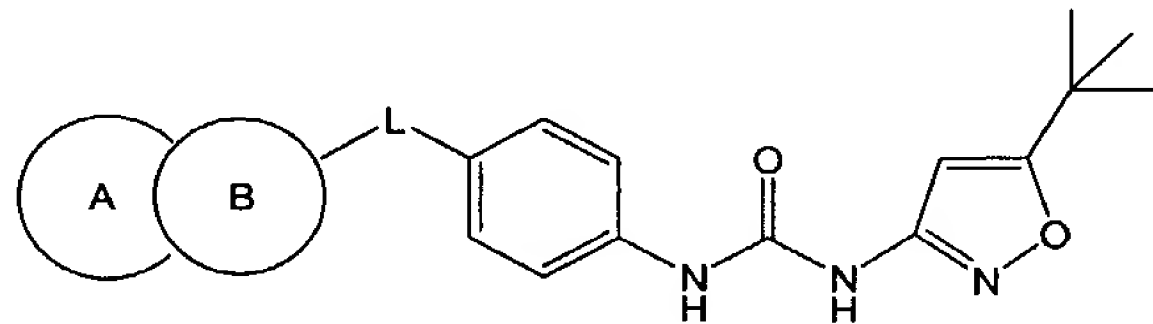
wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-C(O)NH-$, $-C(O)-$, $-NH-$, $-O-$, $-S-$, $-O(\text{substituted or unsubstituted alkylene})-$, $-N(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkenylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkenylene})-$, $-C(O)(\text{substituted or unsubstituted alkenylene})-$, and $-NHC(O)(\text{substituted or unsubstituted alkylene})S(\text{substituted or unsubstituted alkylene})C(O)NH-$; and

T is a mono-, bi-, or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

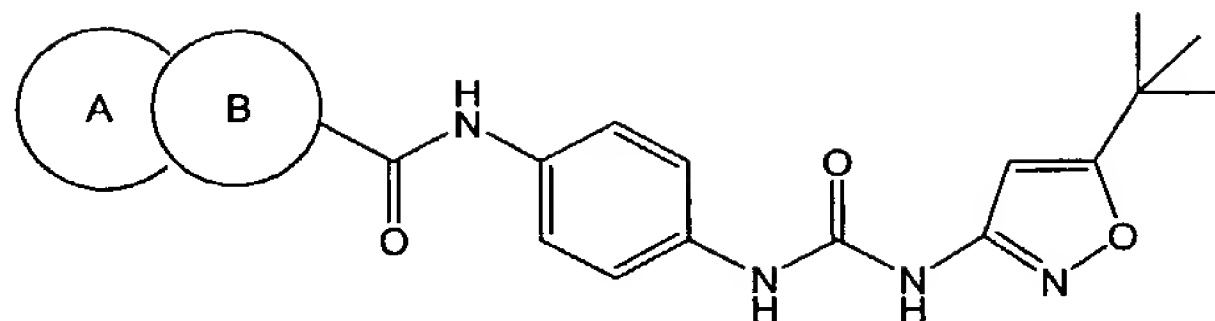
In some embodiments, T is  wherein A is a substituted or unsubstituted five or six-membered heterocyclyl, aryl, or heteroaryl; and B is a substituted or unsubstituted five or six-membered heterocyclene, arylene, or heteroarylene, wherein A and B together form a fused two ring moiety.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



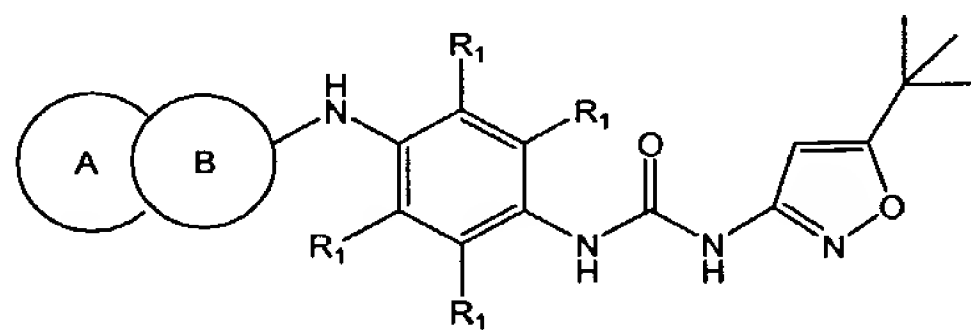
In some embodiments, L of said compound is a covalent bond, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-NHC(O)-$, $-NHC(O)(\text{substituted or unsubstituted alkylene})-$, $-NH-$, or $-O(\text{substituted or unsubstituted alkylene})-$.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



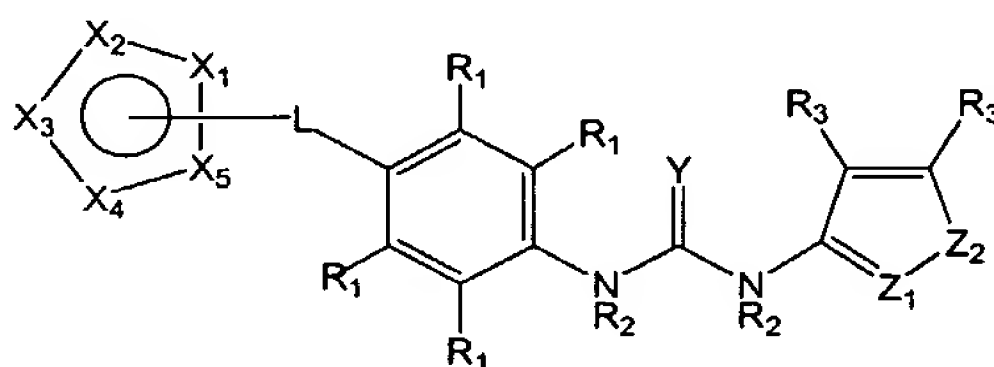
In some embodiments, B of said compound is a substituted or unsubstituted five-membered arylene or heteroarylene. In other embodiments, B is substituted or unsubstituted thiophenylene. In yet other embodiments, B is substituted or unsubstituted imidazolylene. In still other embodiments, B is substituted or unsubstituted pyrrolylene. In other embodiments, B of said compound is a substituted or unsubstituted 6-membered arylene or heteroarylene. In some embodiments, B is substituted or unsubstituted phenylene. In other embodiment, B is substituted or unsubstituted pyridinylene, pyrimidinylene, or pyridazine.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



In some embodiments, B of said compound is a substituted or unsubstituted six-membered heteroarylene. In some embodiments, said six-membered heteroarylene is substituted or unsubstituted pyrimidinylene. In other embodiments, L of said compound $-\text{OCH}_2-$. In some embodiments, L of said compound is $-\text{C}(\text{O})\text{NH}$.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



wherein:

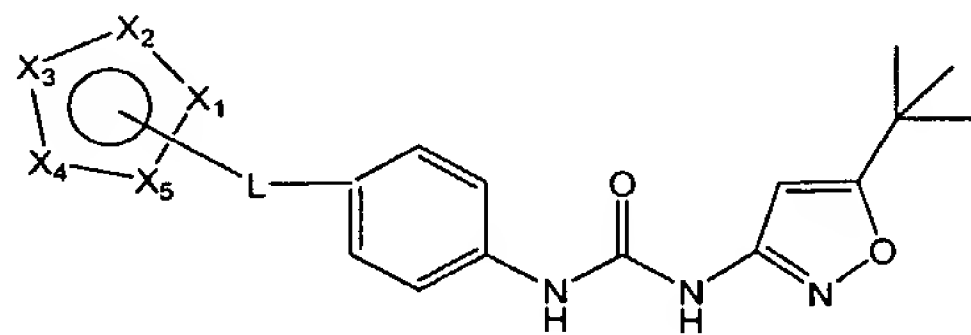
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-C(O)NH-$, $-C(O)-$, $-NH-$, $-O-$, $-S-$, $-O(\text{substituted or unsubstituted alkylene})-$, $-N(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkenylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkenylene})-$, $-C(O)(\text{substituted or unsubstituted alkenylene})-$, and $-NHC(O)(\text{substituted or unsubstituted alkylene})S(\text{substituted or unsubstituted alkylene})C(O)NH-$; and

each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where

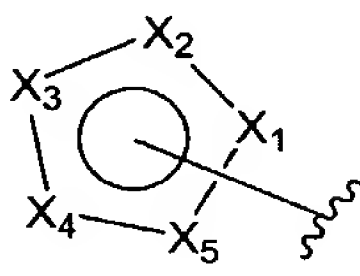
each R is independently H, halogen, substituted or unsubstituted alkyl, $-OH$, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d$, $C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$ or $-C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

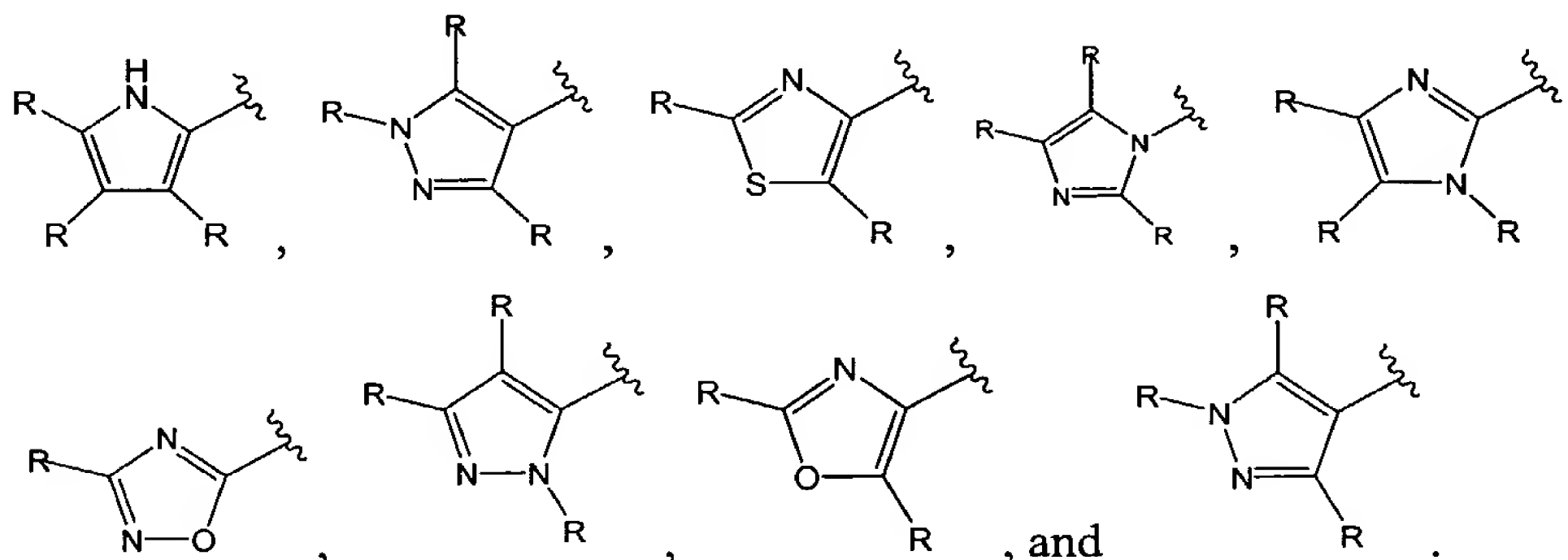
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

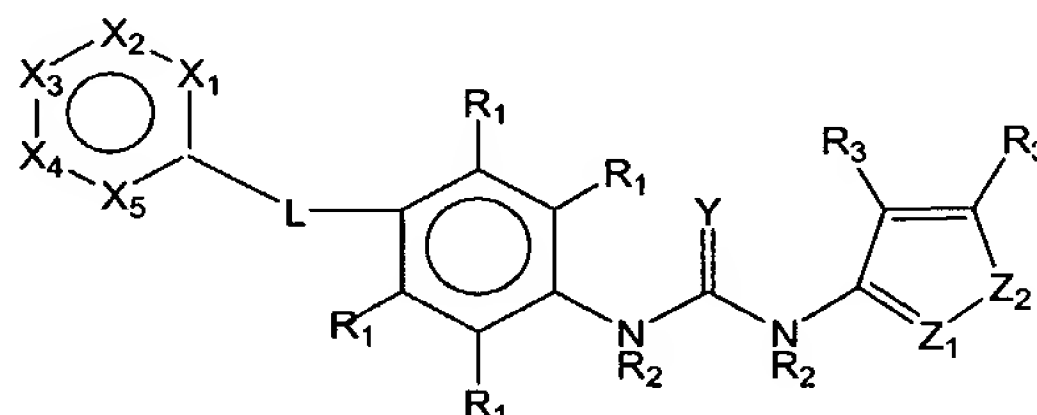


In some embodiments, L of said compound is a covalent bond, -C(O)NH-, or -O(substituted

or unsubstituted alkylene)-. In other embodiments,  of said compound is selected from the group consisting of:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



10 wherein:

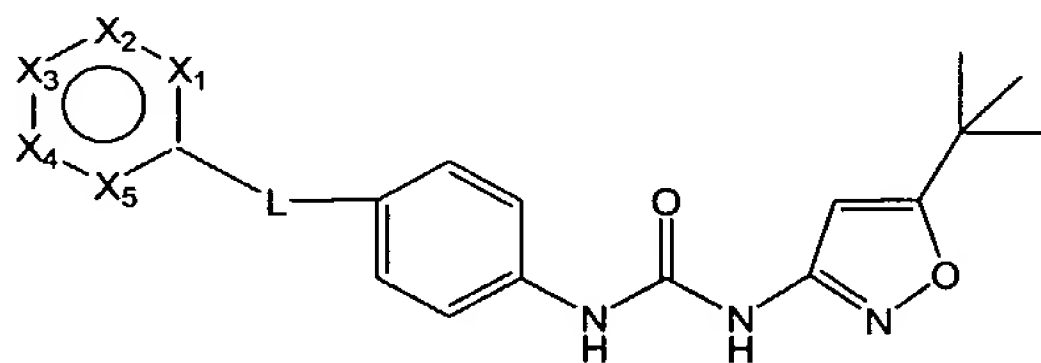
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, -C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

each of X_1 - X_5 is independently C, CR, N-O, or N, wherein no more than two of X_1 - X_5 is N, where

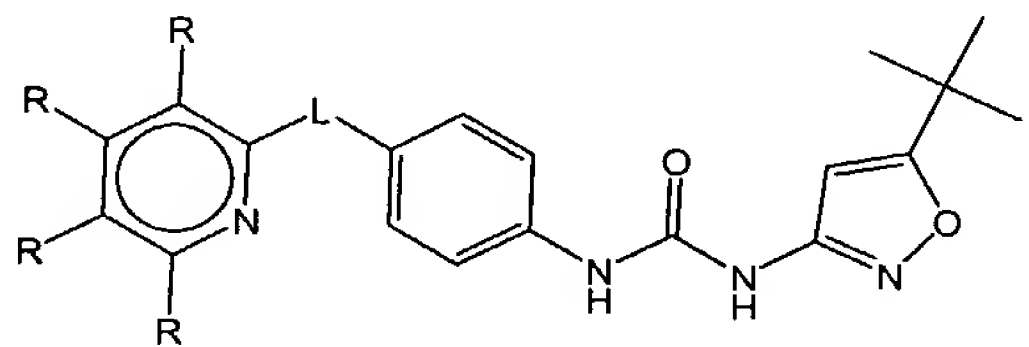
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -S(O)_j R_d where j is 1 or 2, -NR_d C(O) R_d , -C(O)₂ R_d , -C(O)N(R_d)₂ or -C(O) R_d , or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

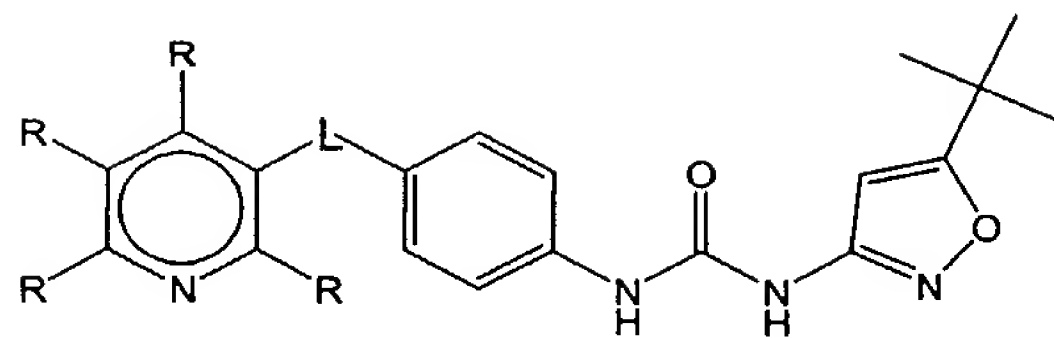
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



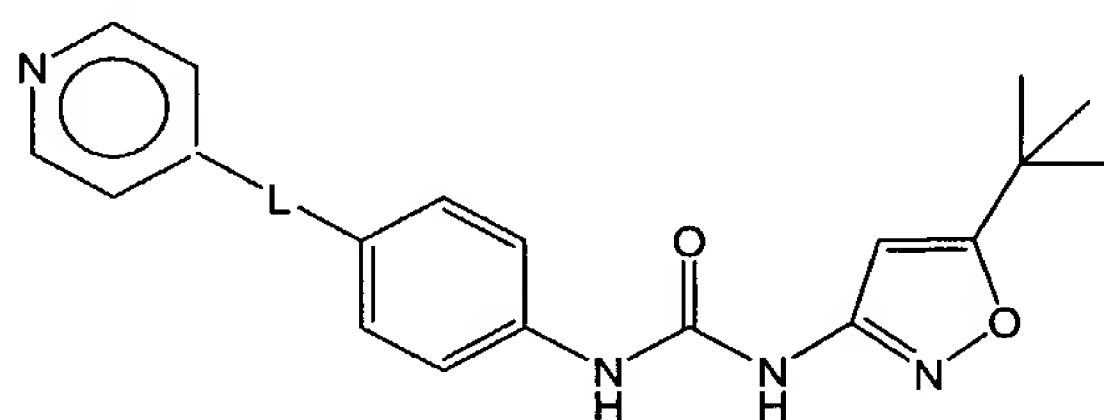
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

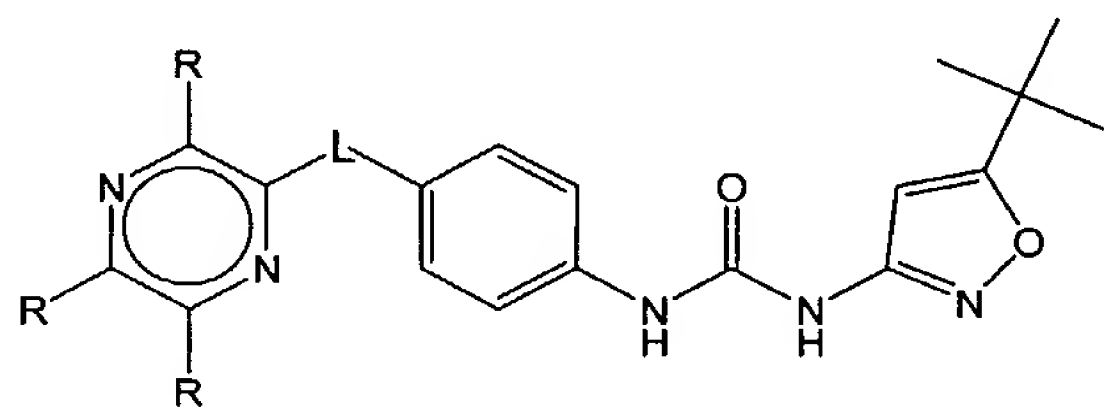


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

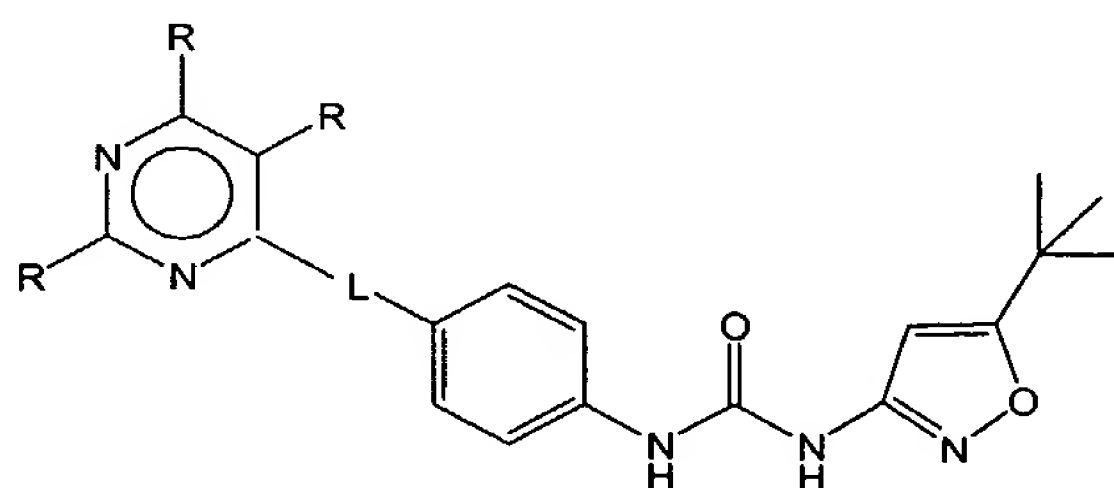


wherein L is -O(substituted or unsubstituted alkylene)- or -C(O)(substituted or unsubstituted alkenylene)-.

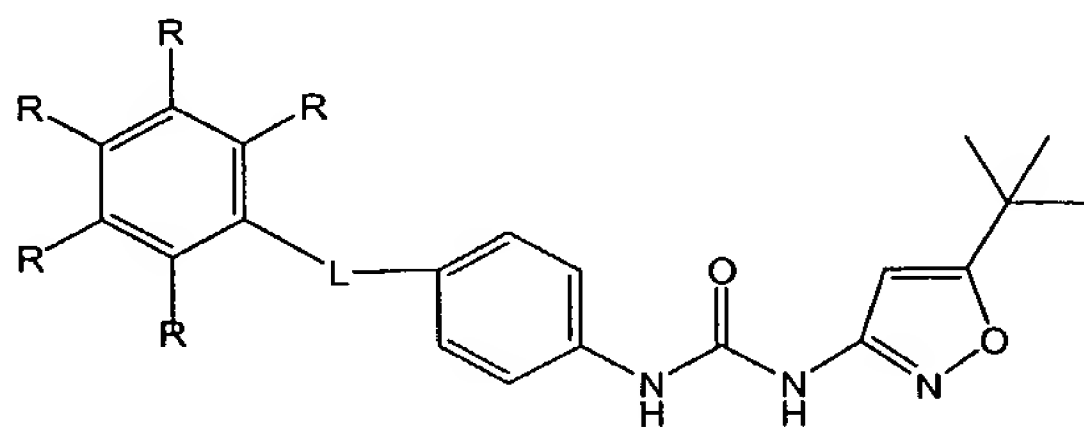
Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

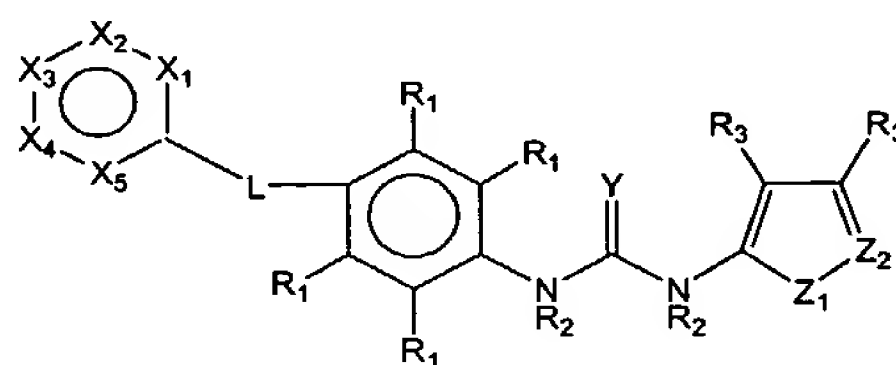


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



- 5 In some embodiments, L of said compound is -O(substituted or unsubstituted alkylene)- or -O(substituted or unsubstituted alkenylene)-. In other embodiments, L of said compound is -NHC(O)-. In yet other embodiments, L of said compound is a covalent bond, substituted or unsubstituted alkylene, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -NH(alkylene)-, -NHC(O)CH₂SCH₂C(O)NH-, and -NHC(O)(substituted alkylene)S-.
- 10

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



15 wherein:

- L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, -C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-,
- 20

and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

each of X_1 - X_5 is independently C, CR, or N, wherein no more than two of X_1 - X_5 is N, where

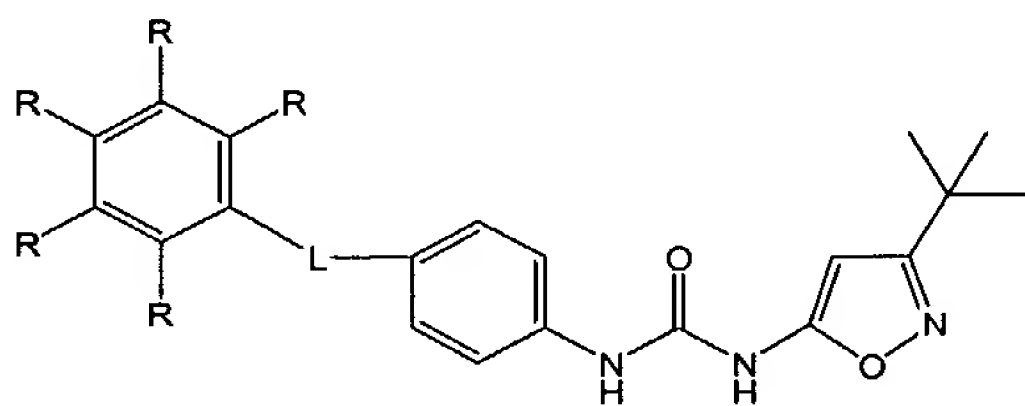
5 each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -S(O)_j R_d where j is 1 or 2, -NR_d C(O) R_d , -C(O)₂ R_d , -C(O)N(R_d)₂ or -C(O) R_d , or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

10 each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

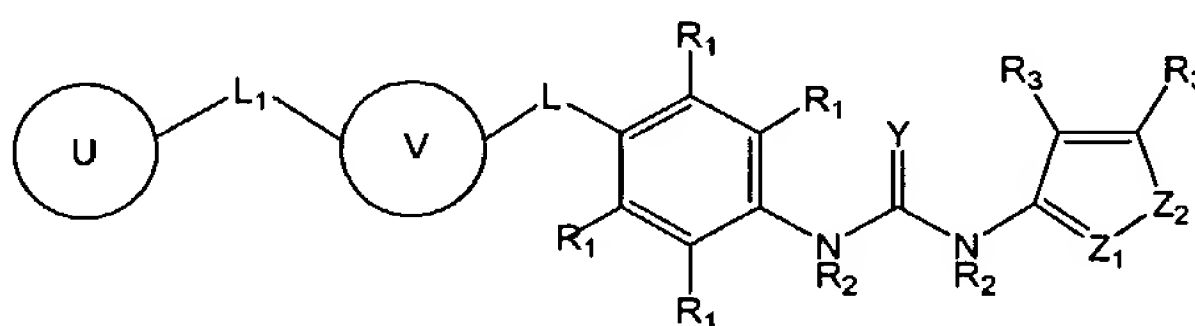
Z_1 is O or S; and

Z_2 is CR₃ or N.

15 Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



20 Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



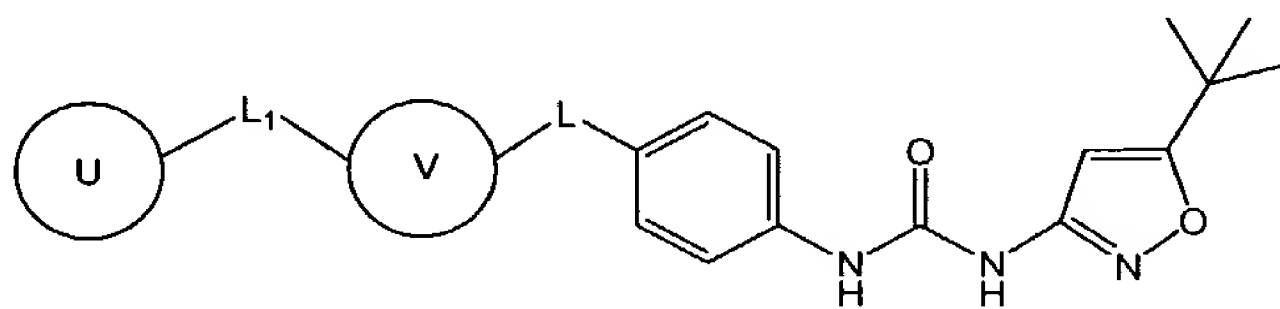
wherein:

each of L and L₁ is independently a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, -C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-;

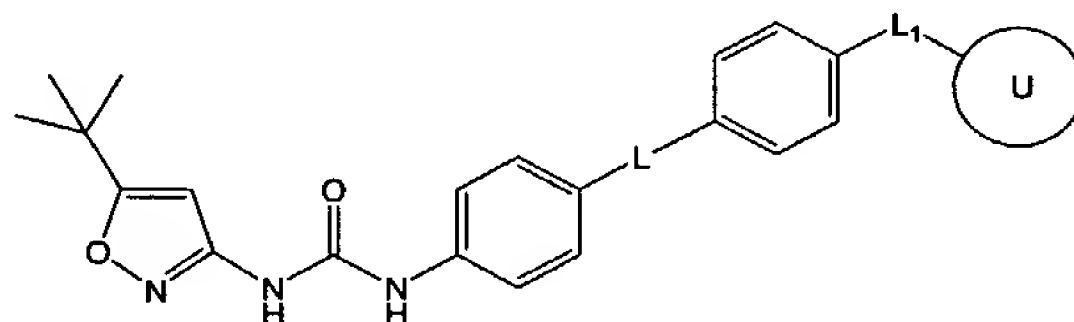
U is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:

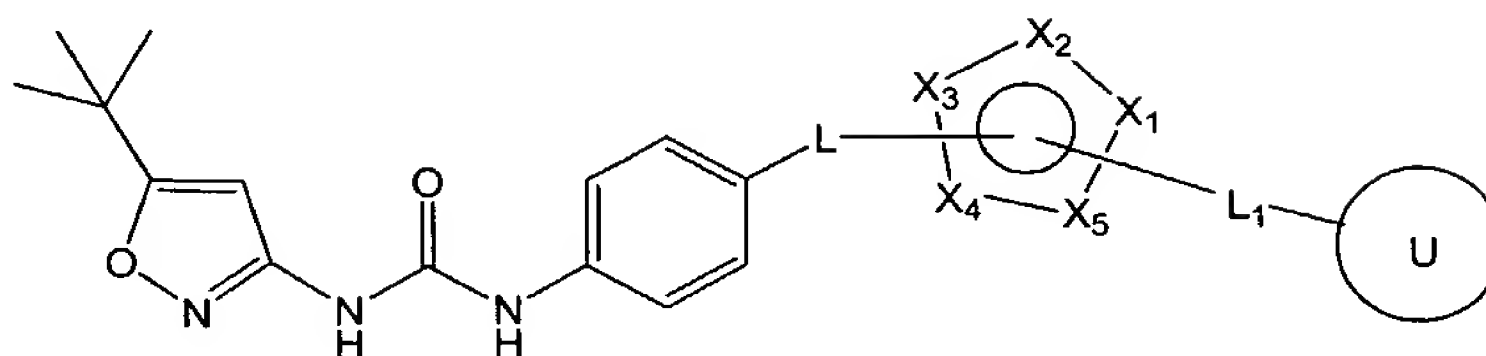


Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding

to the following formula are provided herein:



wherein:

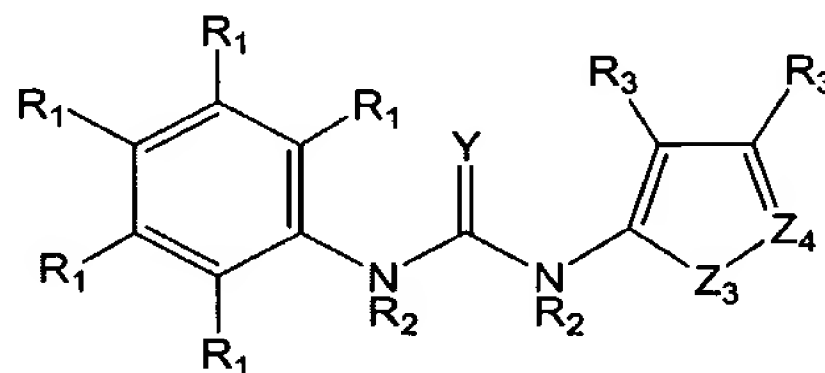
each of X_1 - X_5 is independently C, CR, N, NR, S, or O, wherein no more than
 5 three of X_1 - X_5 is a heteroatom, and no two adjacent ring atoms are O or S; and

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH,
 substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -
 S(O)_j R_d where j is 1 or 2, -NR_d C(O) R_d , -C(O)₂ R_d , -C(O)N(R_d)₂
 or -C(O) R_d , or two adjacent R's are taken together to form a substituted or
 10 unsubstituted aryl or hetroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or
 unsubstituted heteroaryl.

In some embodiments, U is a substituted or unsubstituted five-membered heteroaryl,
 15 substituted or unsubstituted phenyl, or substituted or unsubstituted six-membered heteroaryl.

Methods for modulating FLT-3 kinase, said method comprising administering an
 effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding
 to the following formula are provided herein:



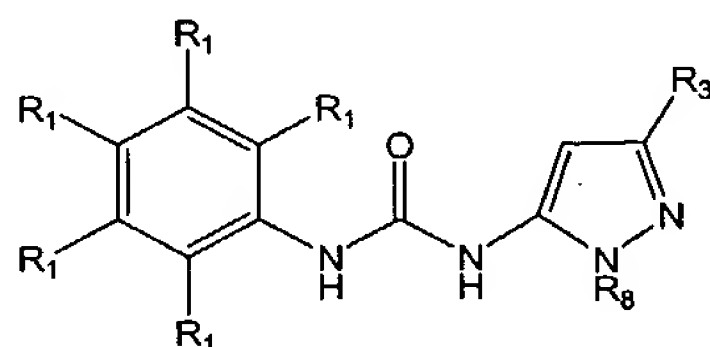
wherein:

Z_3 is NR₈, O, or S;

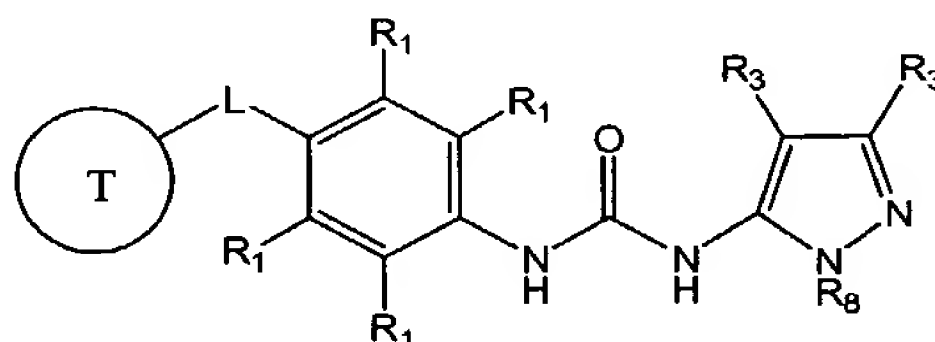
Z_4 is N or CR₈; and

R_8 is H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl.

Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



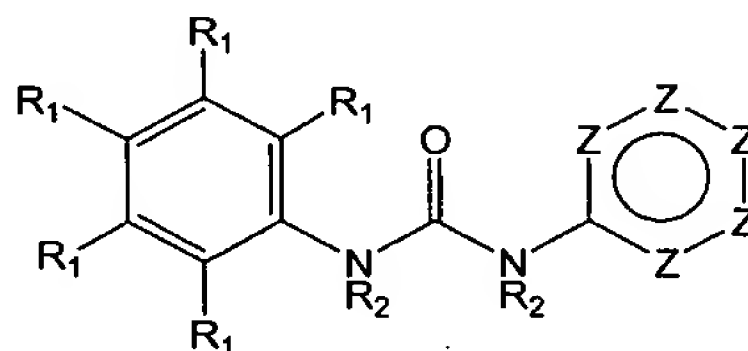
wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-C(O)NH-$, $-C(O)-$, $-NH-$, $-O-$, $-S-$, $-O(\text{substituted or unsubstituted alkylene})-$, $-N(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkenylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkenylene})-$, $-C(O)(\text{substituted or unsubstituted alkenylene})-$, and $-NHC(O)(\text{substituted or unsubstituted alkylene})S(\text{substituted or unsubstituted alkylene})C(O)NH-$; and

T is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

Methods for modulating FLT-3 kinase, said method comprising administering an

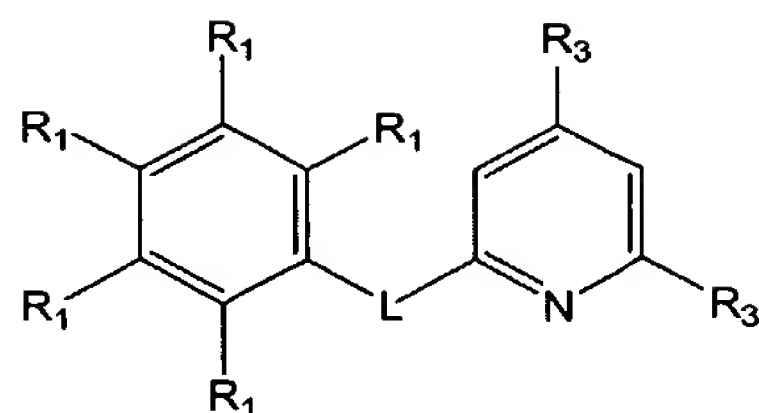
effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



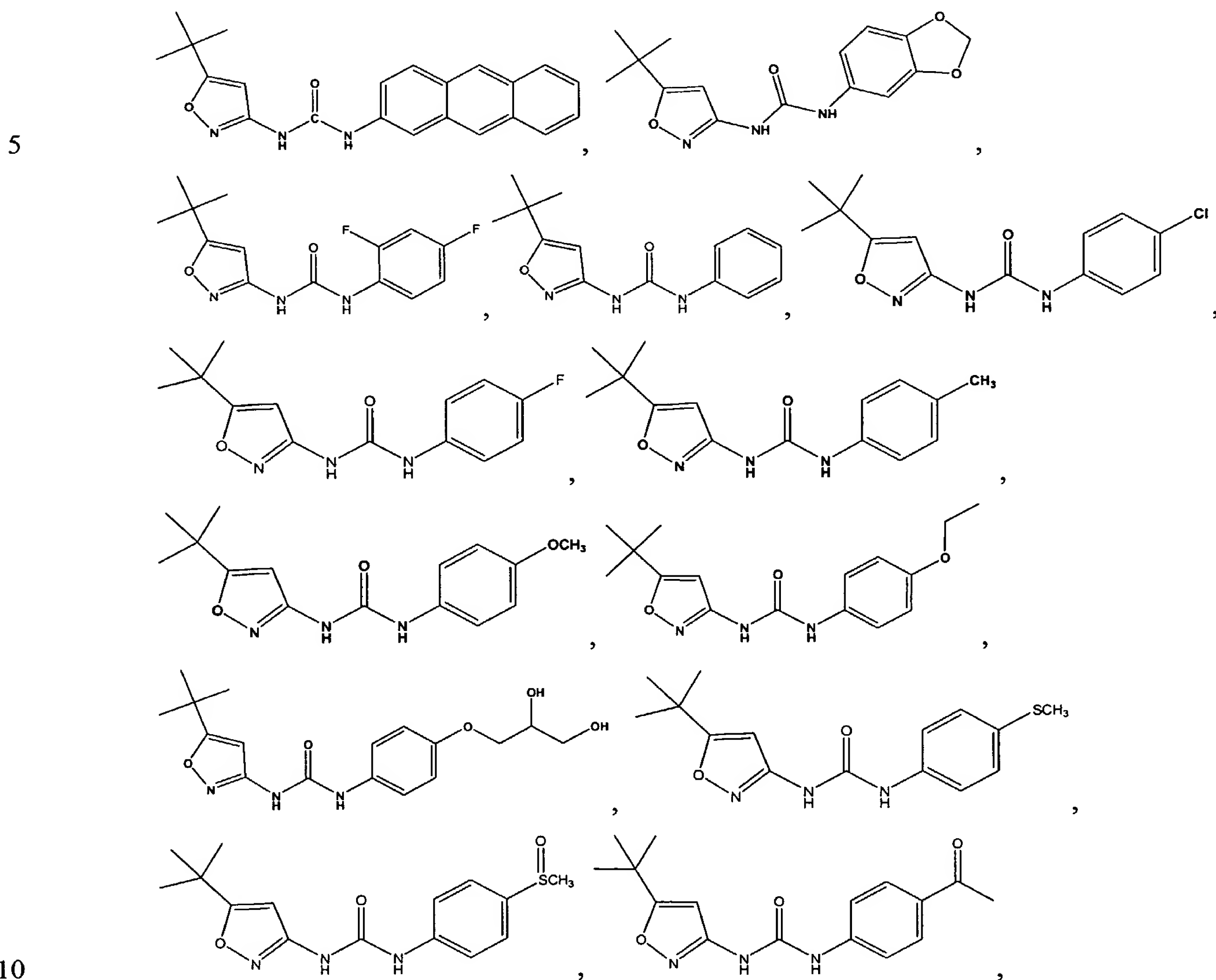
wherein:

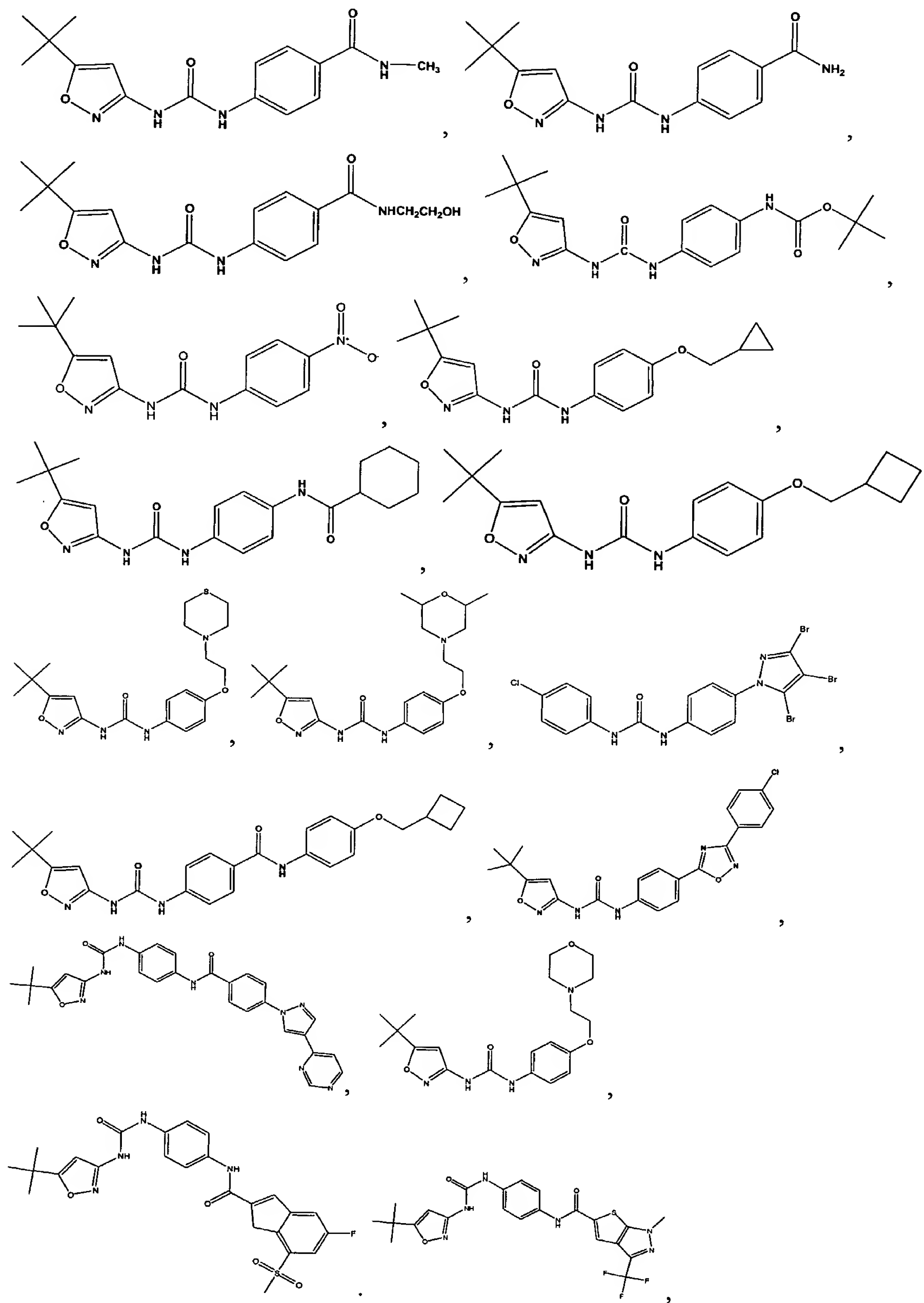
- 5 each Z is independently C, CR₃, N, NR₃, O, or S, provided that no more than two Z's are heteroatoms where
- R₃ is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl.
- 10 each R₂ is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R₂ groups are linked together by an optionally substituted alkylene; and
- 15 each R₁ is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR_c, -OH, -OC(O)R_c, -NO₂, -N(R_c)₂, -SR_c, S(O)_jR_c where j is 1 or 2, -NR_cC(O)R_c, -C(O)N(R_c)₂, C(O)₂R_c, or -C(O)R_c; or two adjacent R₁'s, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where
- 20 each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

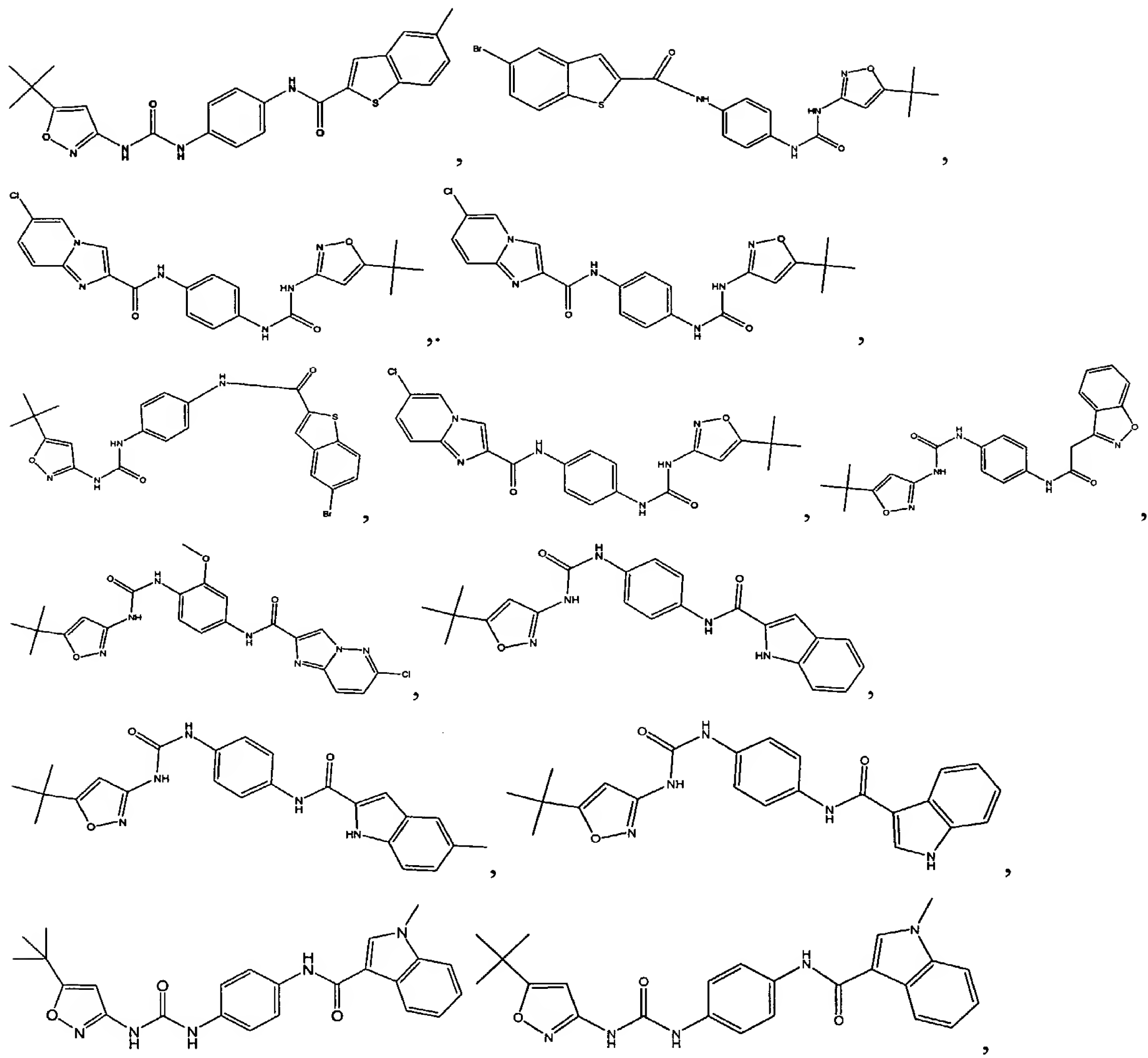
25 Methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following formula are provided herein:



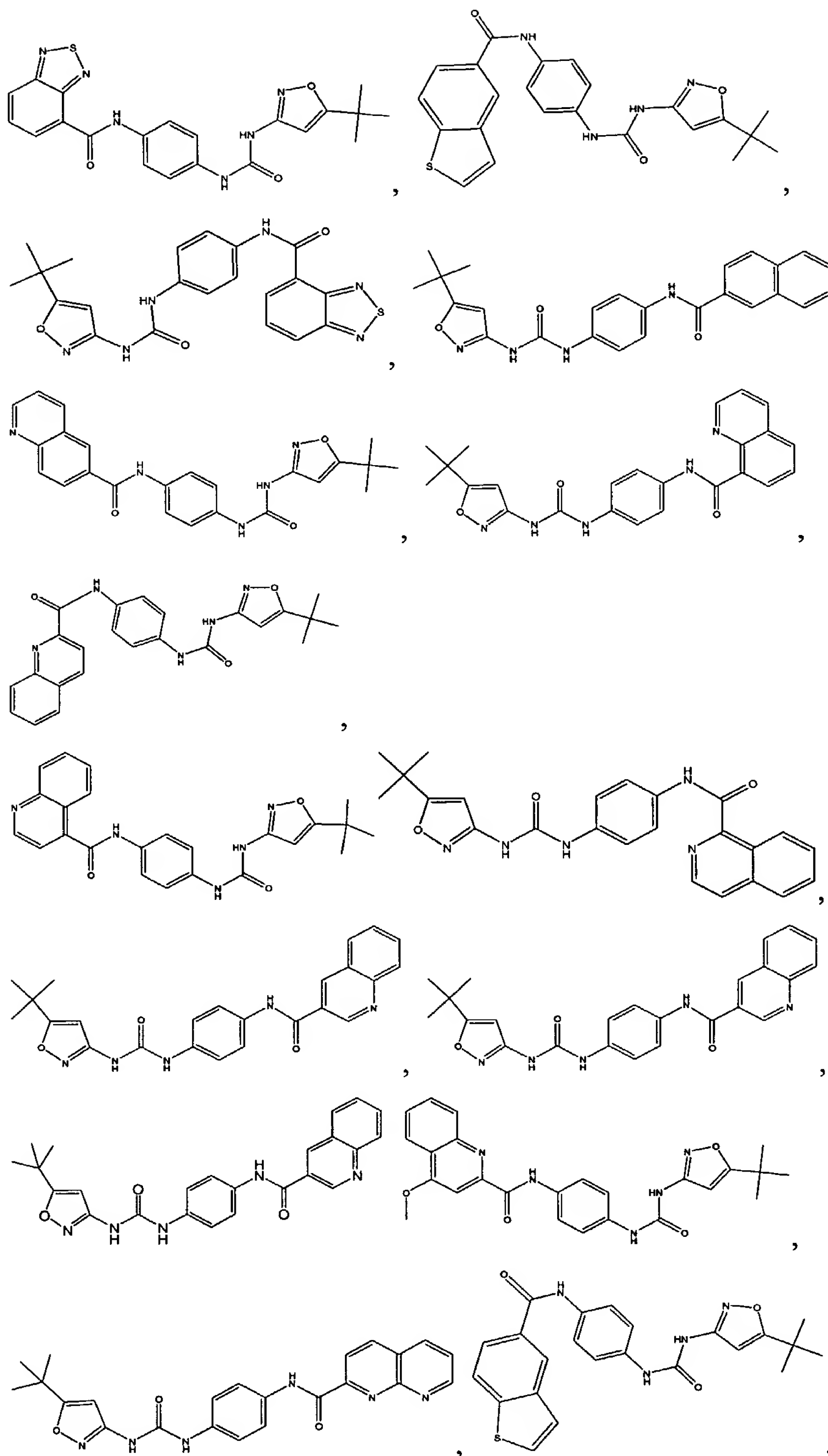
Provided herein are methods for modulating FLT-3 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:



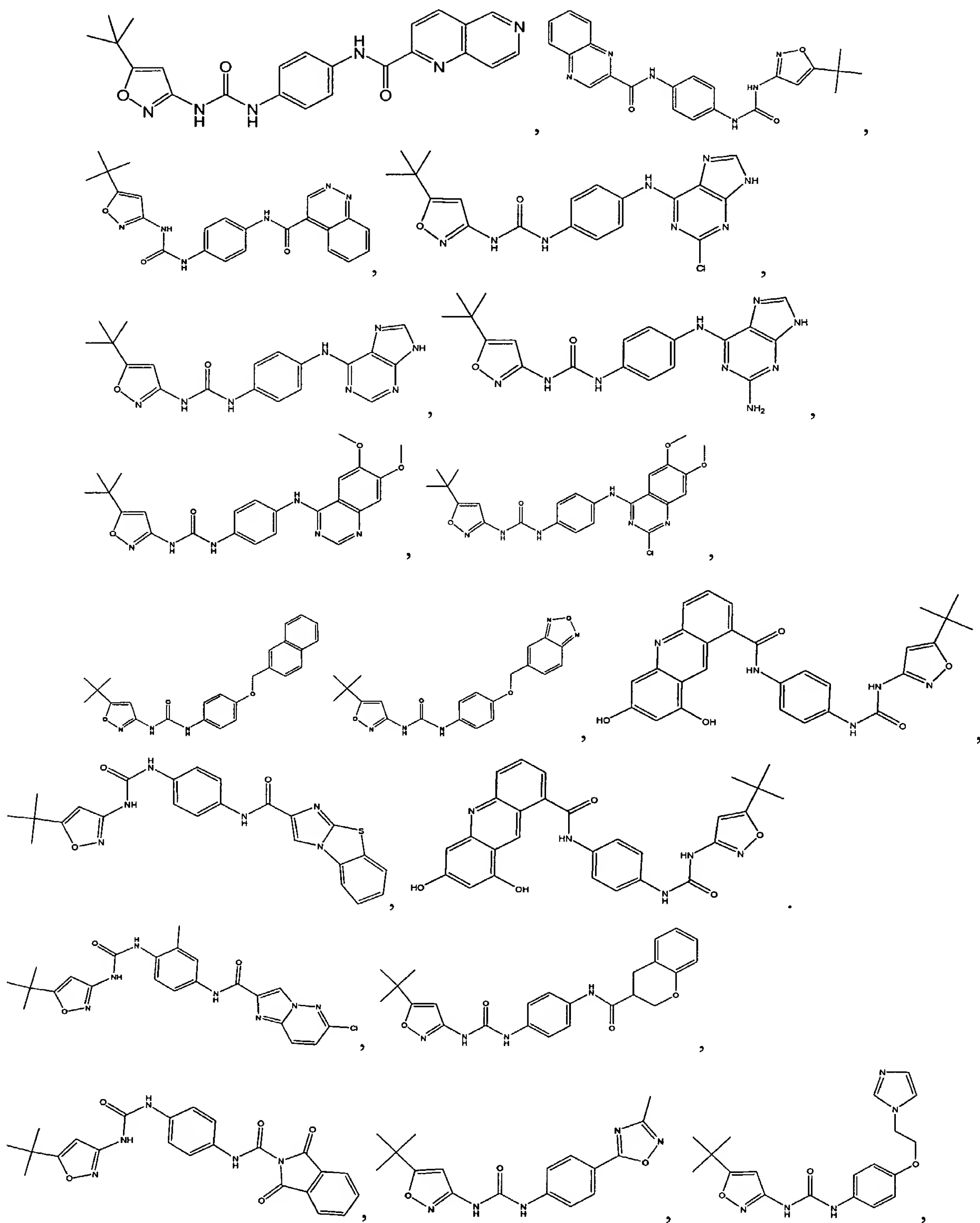


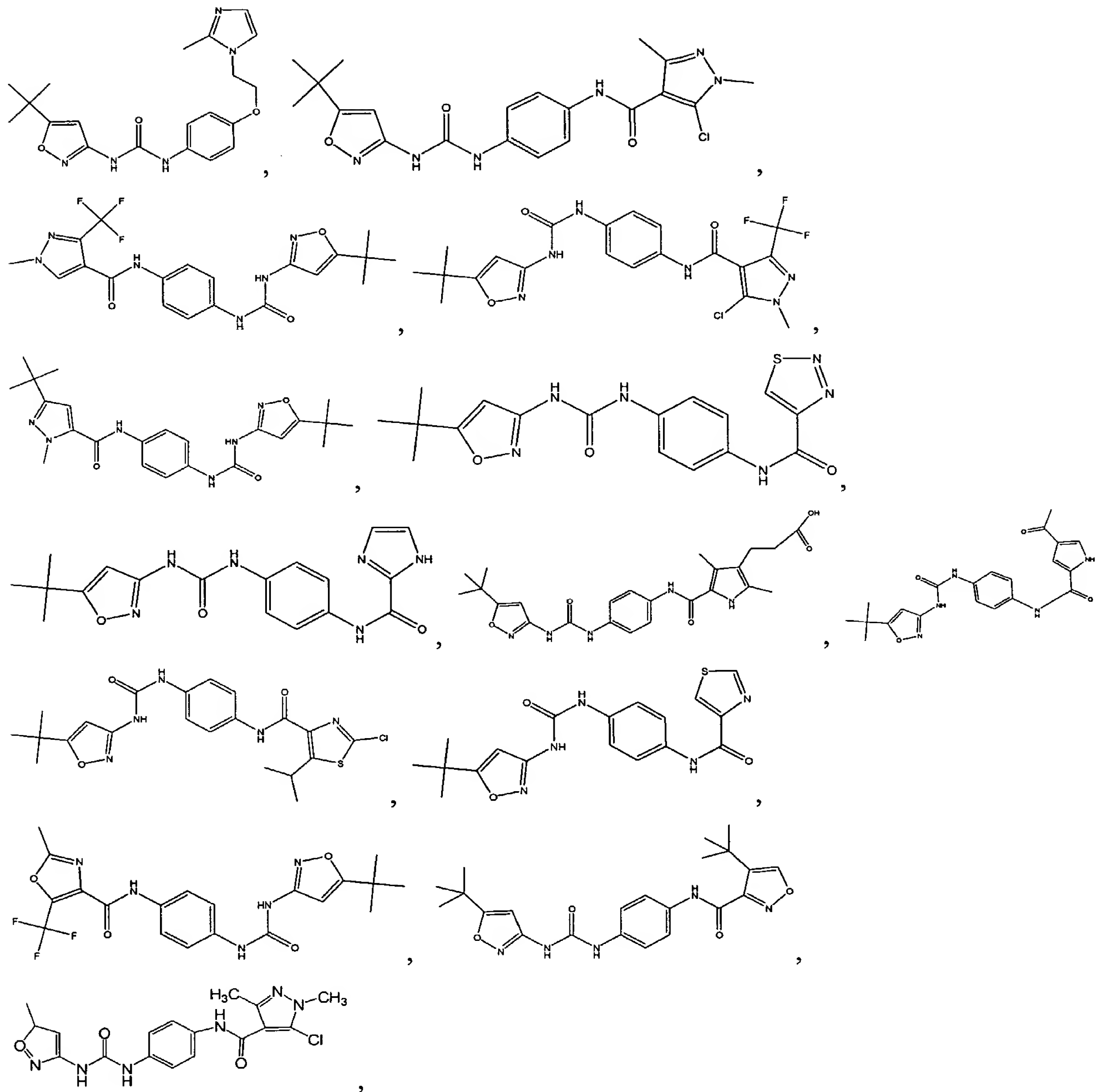


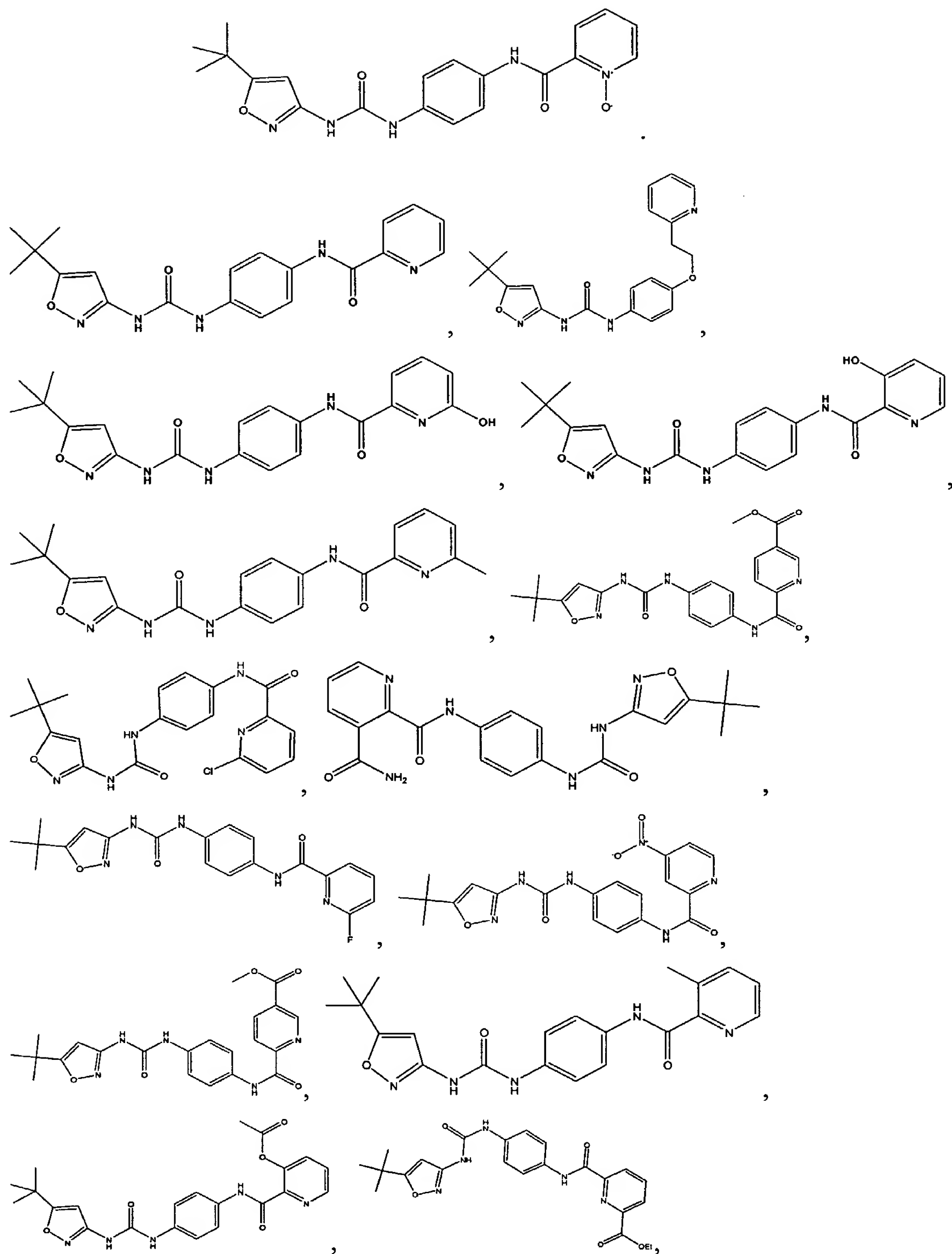
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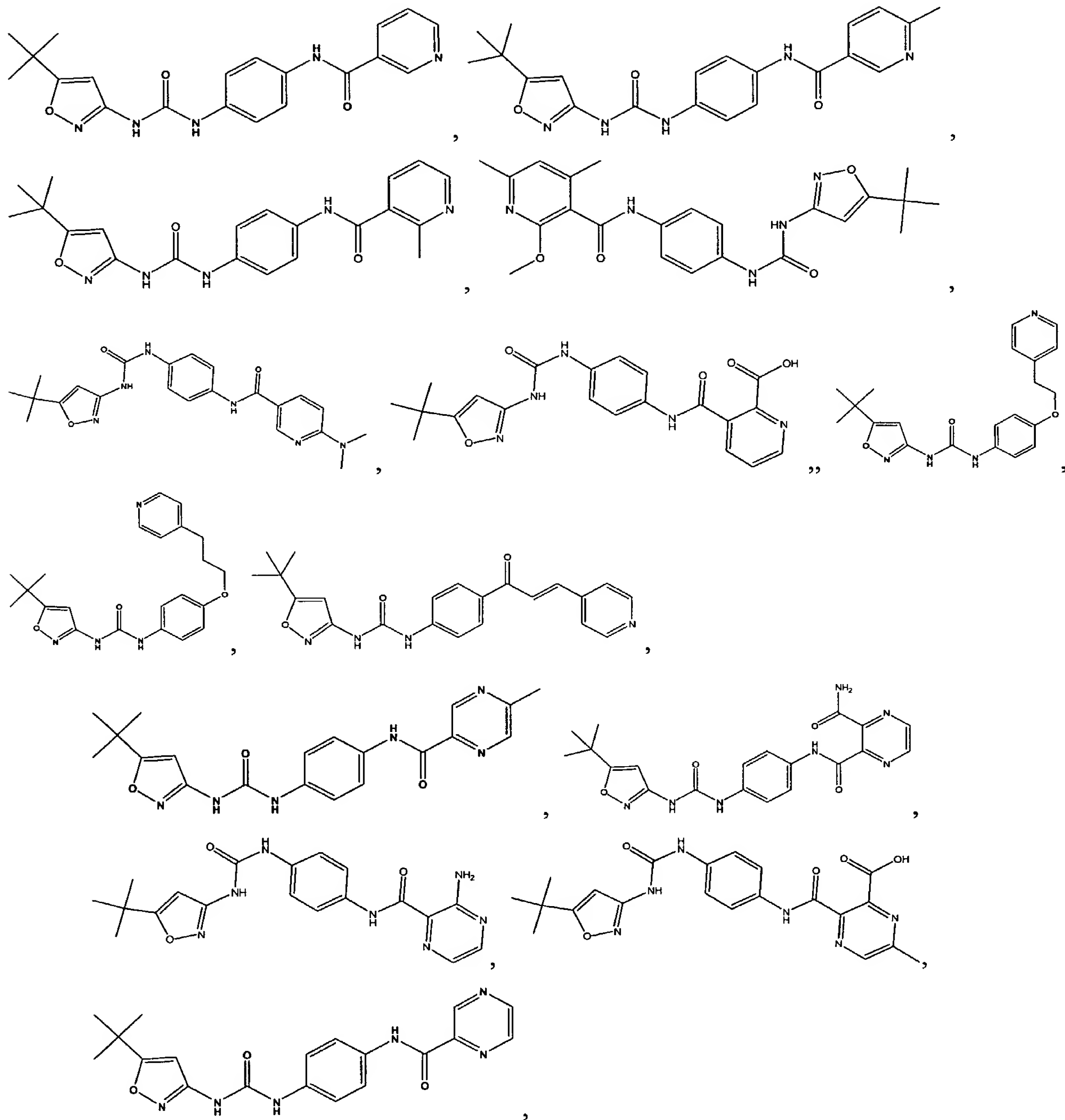


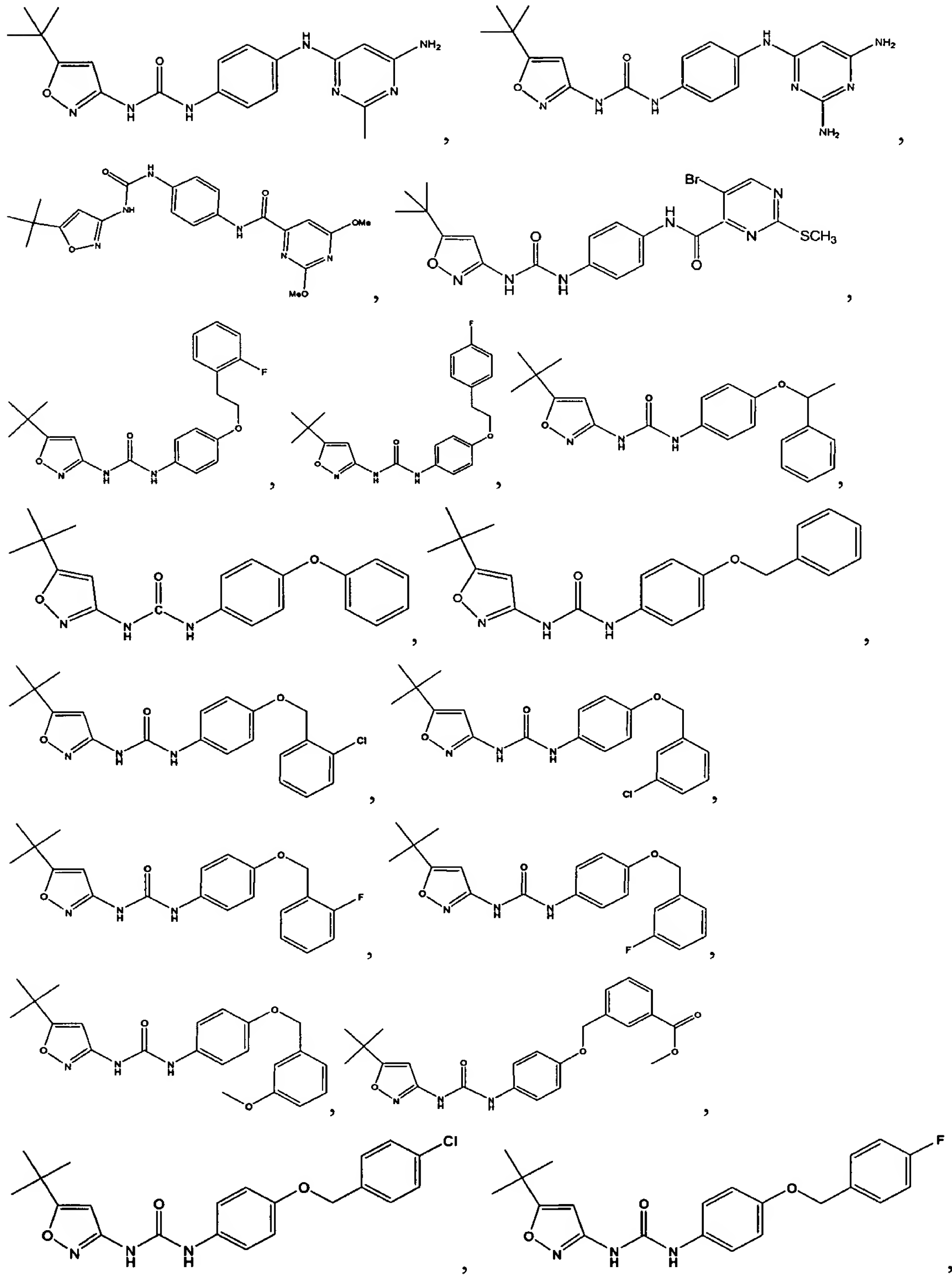
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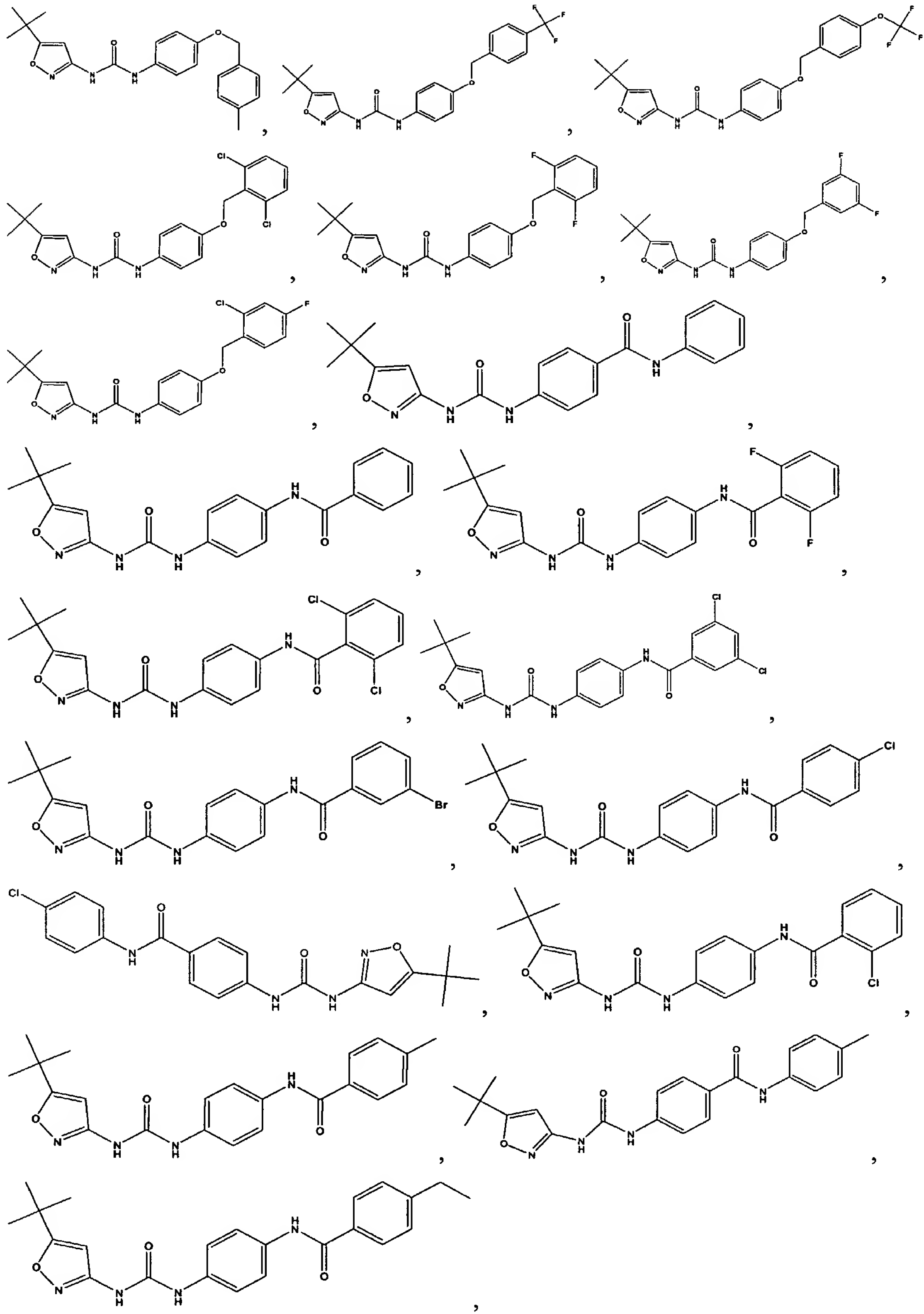


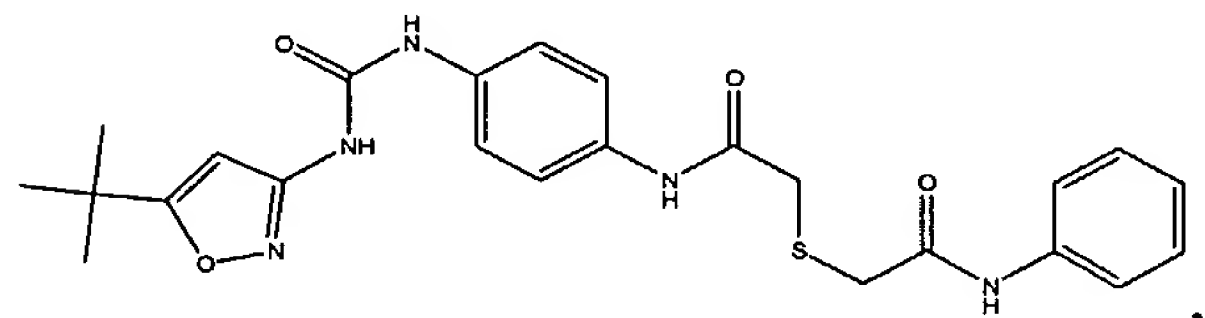
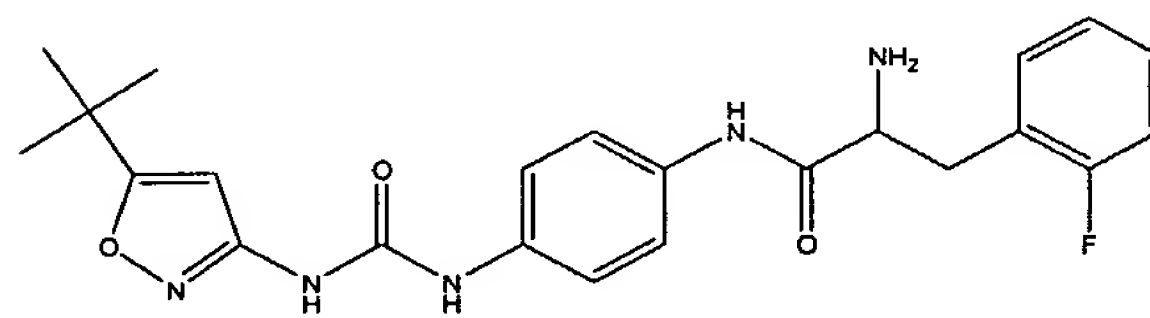
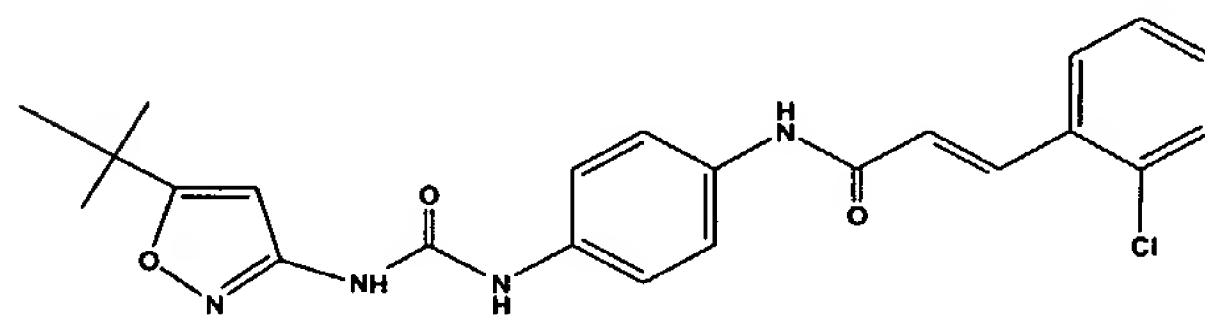
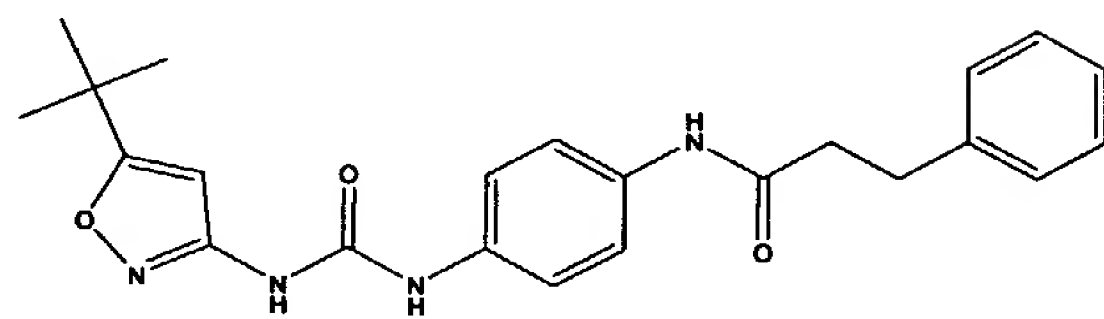
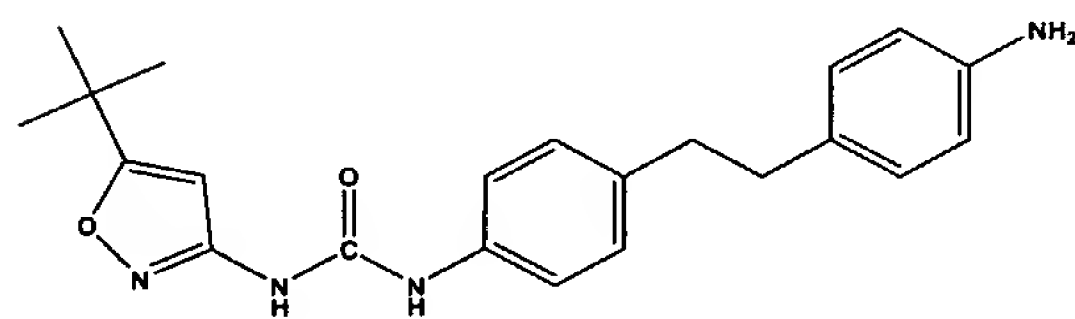
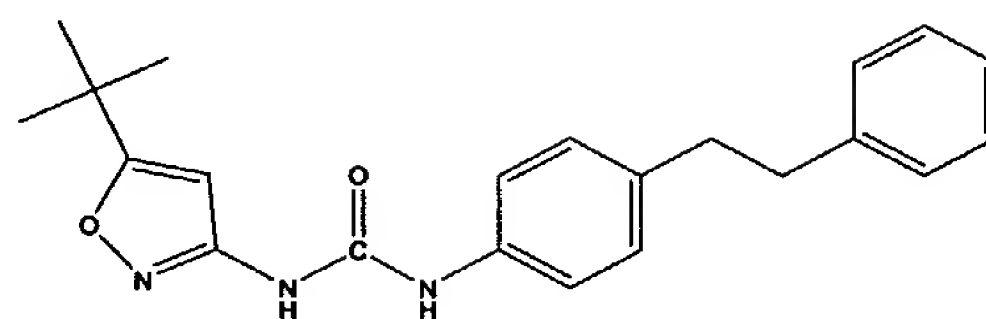
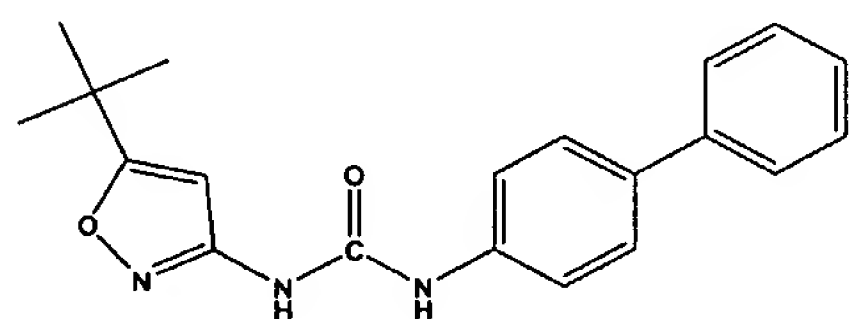
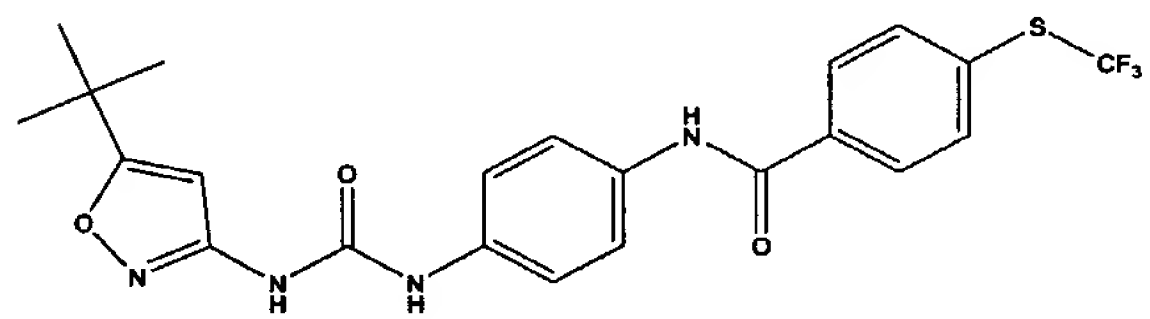
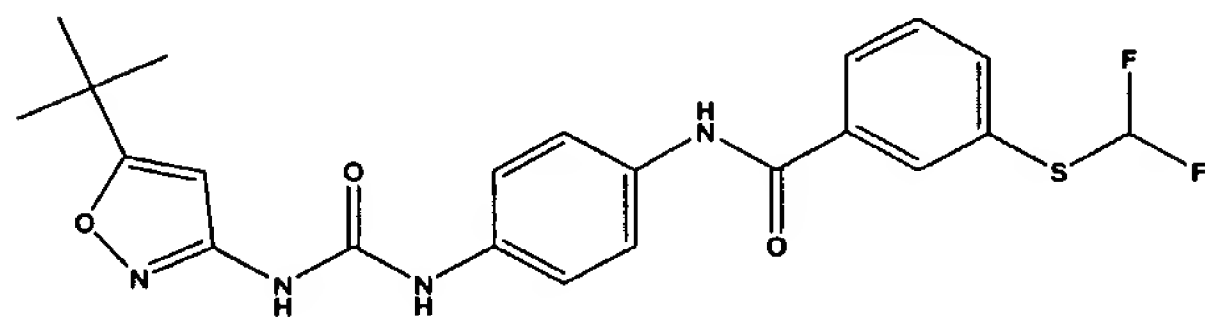
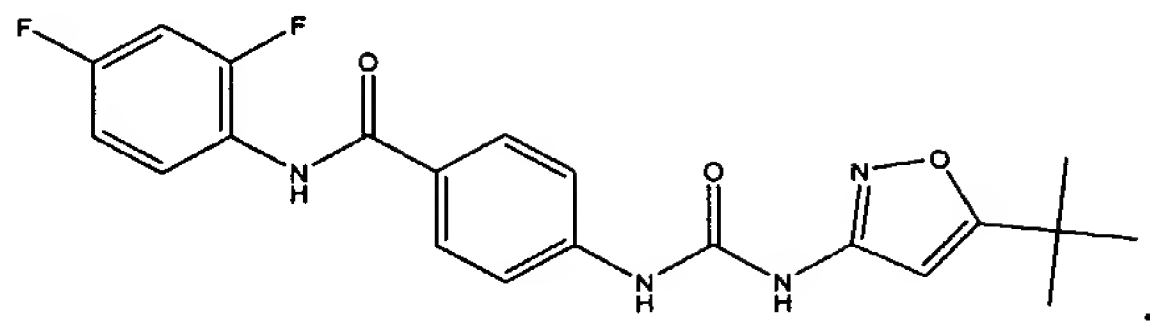


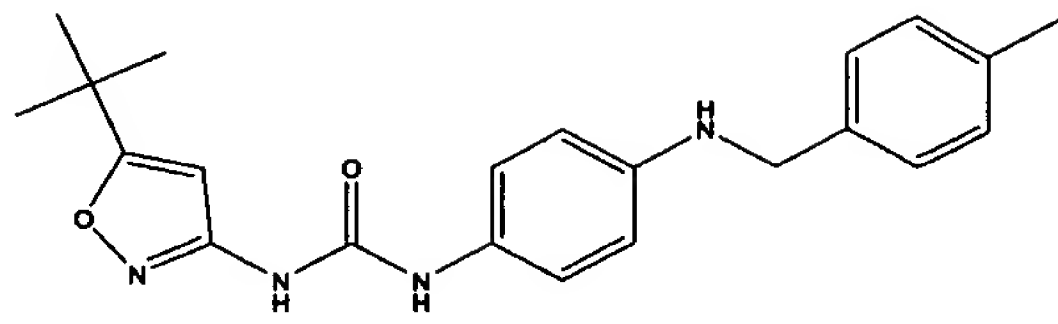




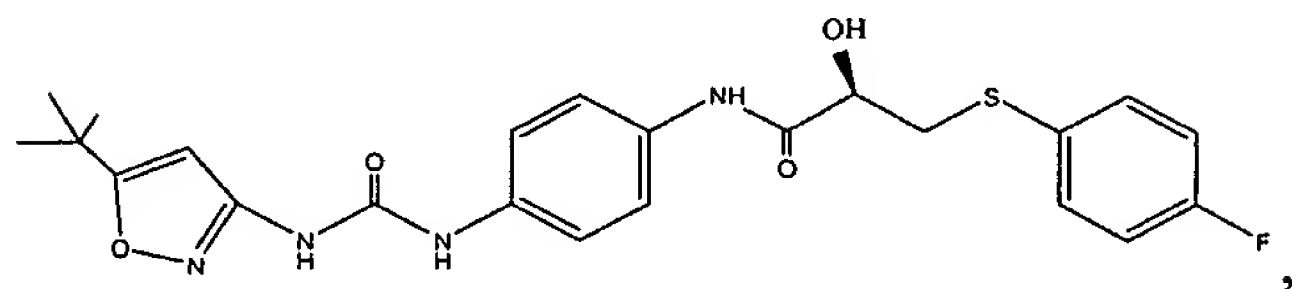




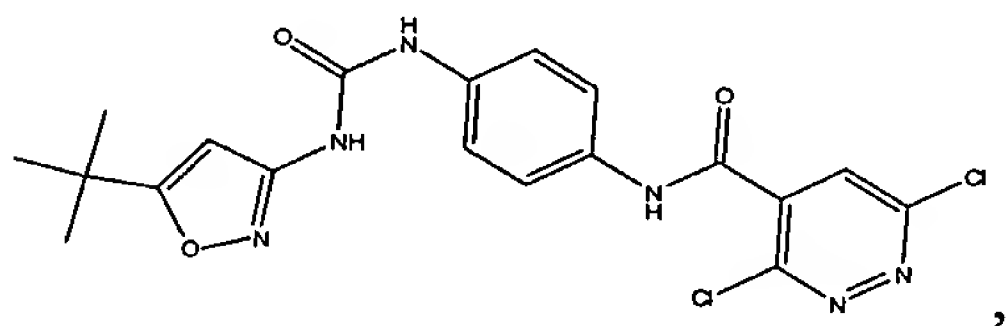




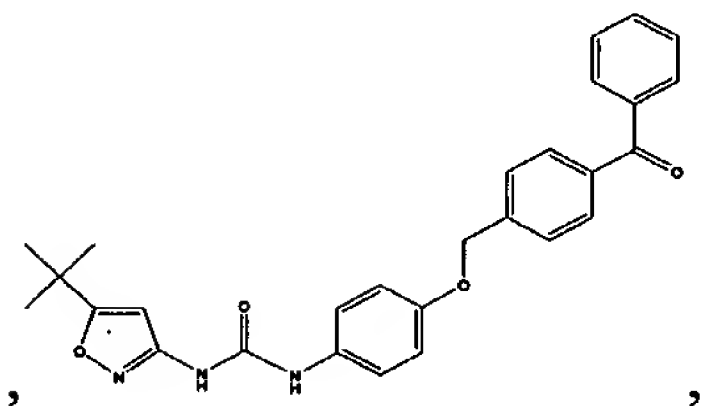
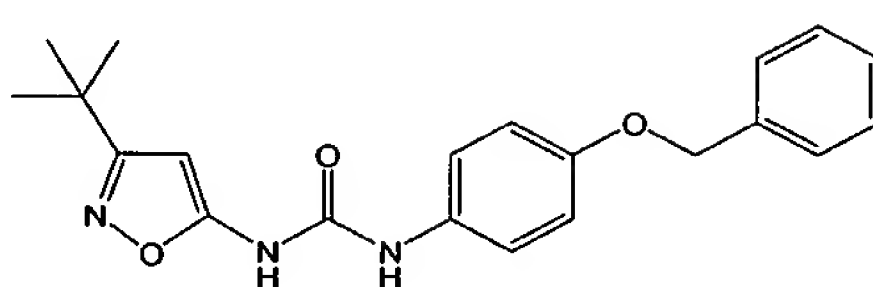
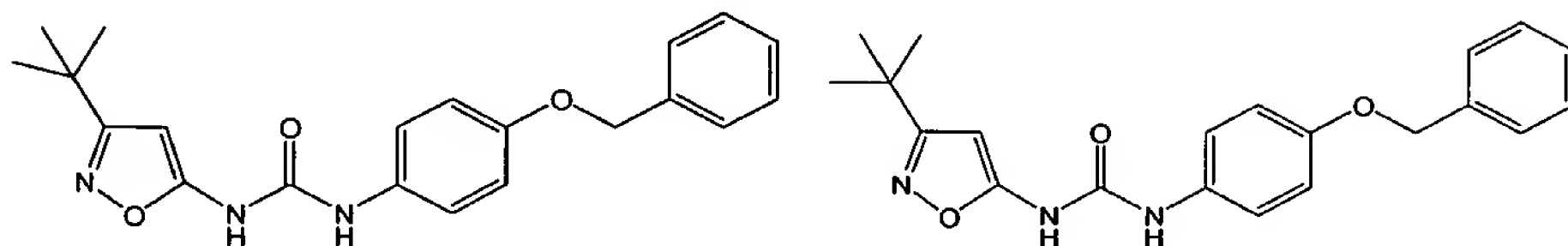
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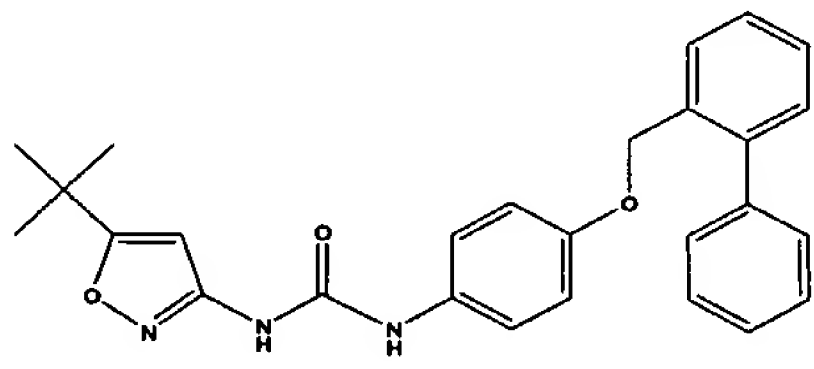
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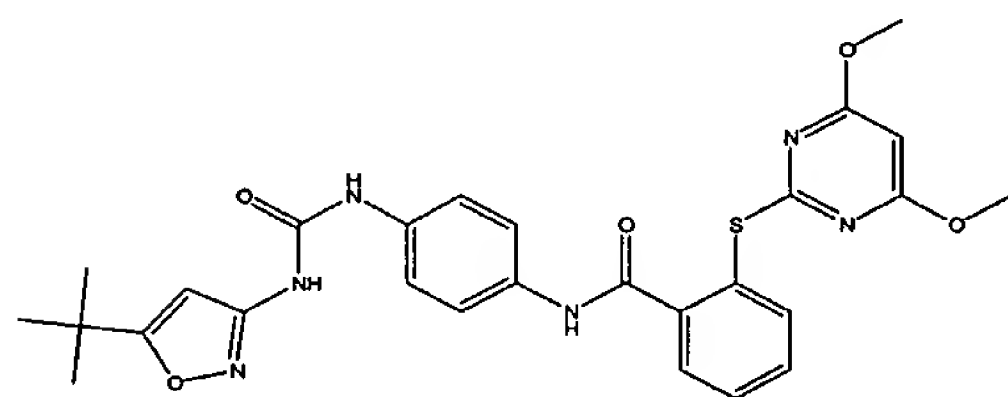
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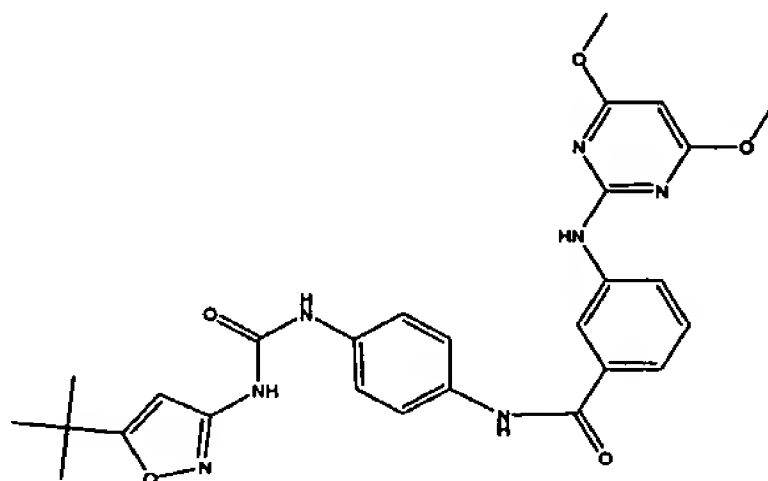
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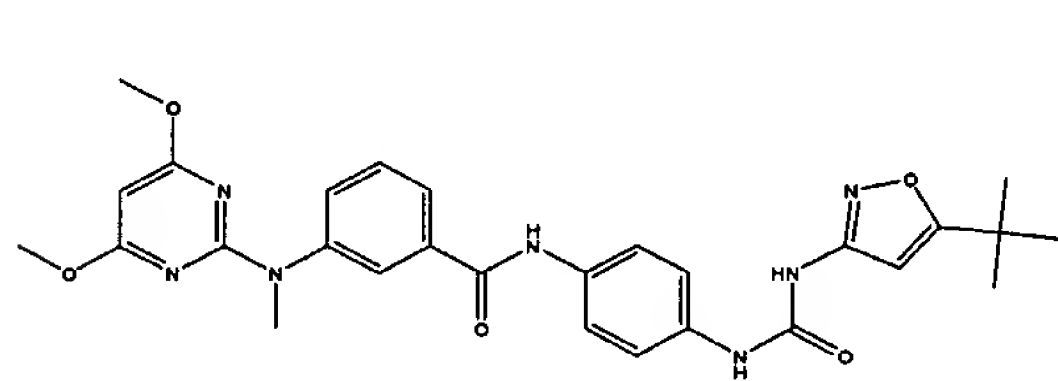
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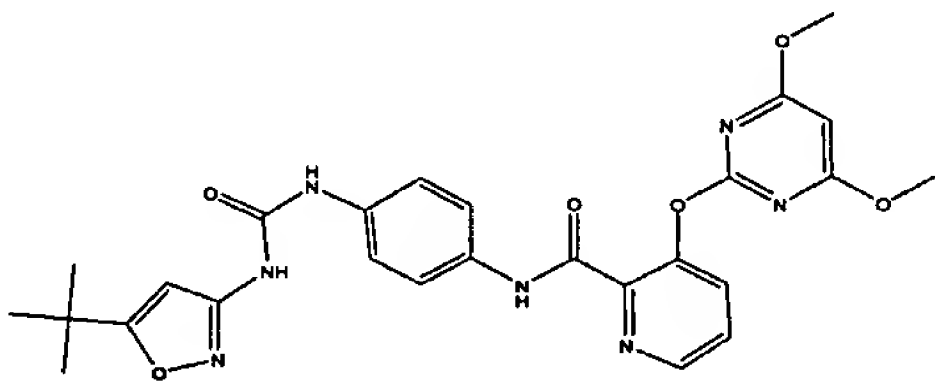
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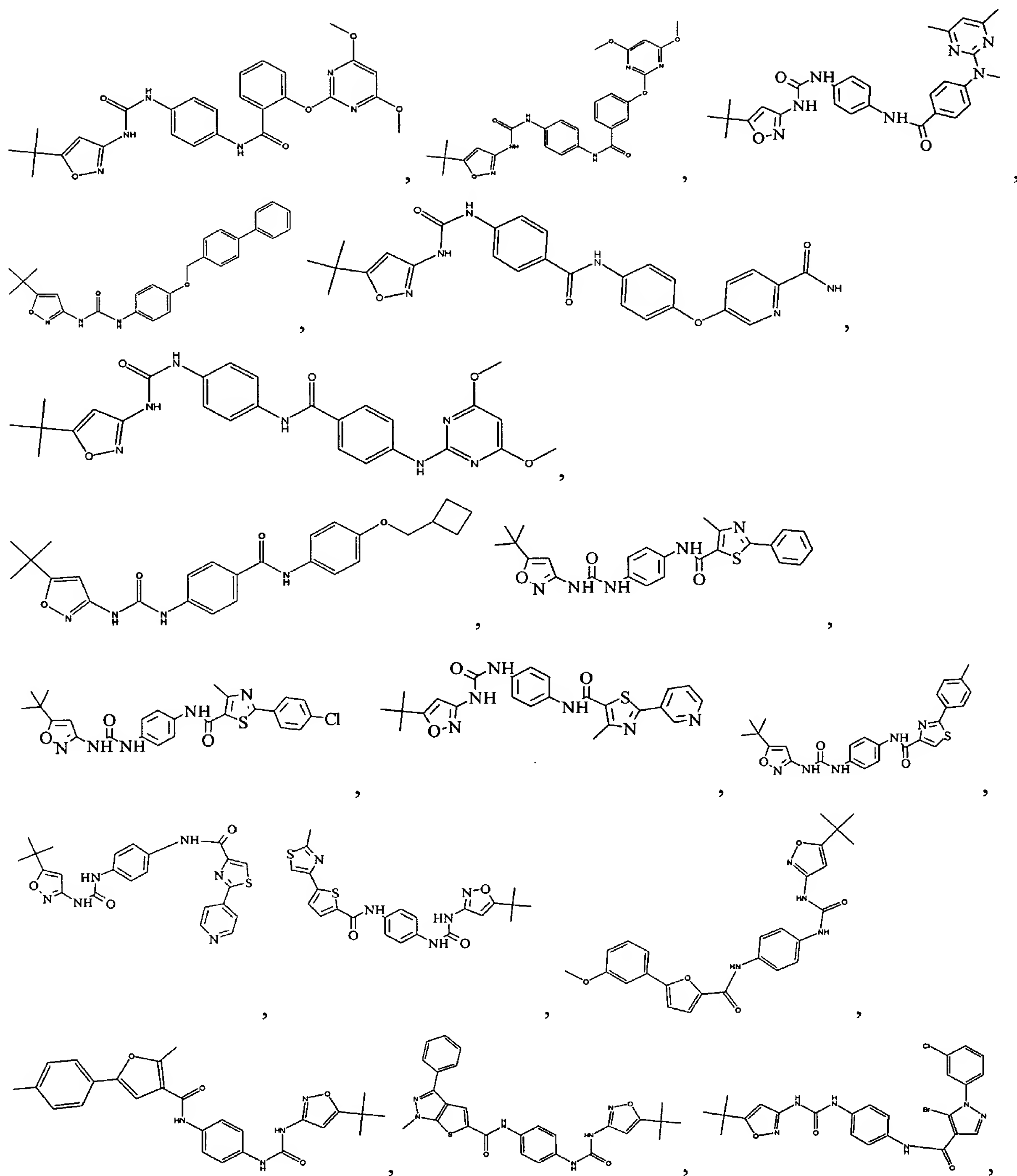


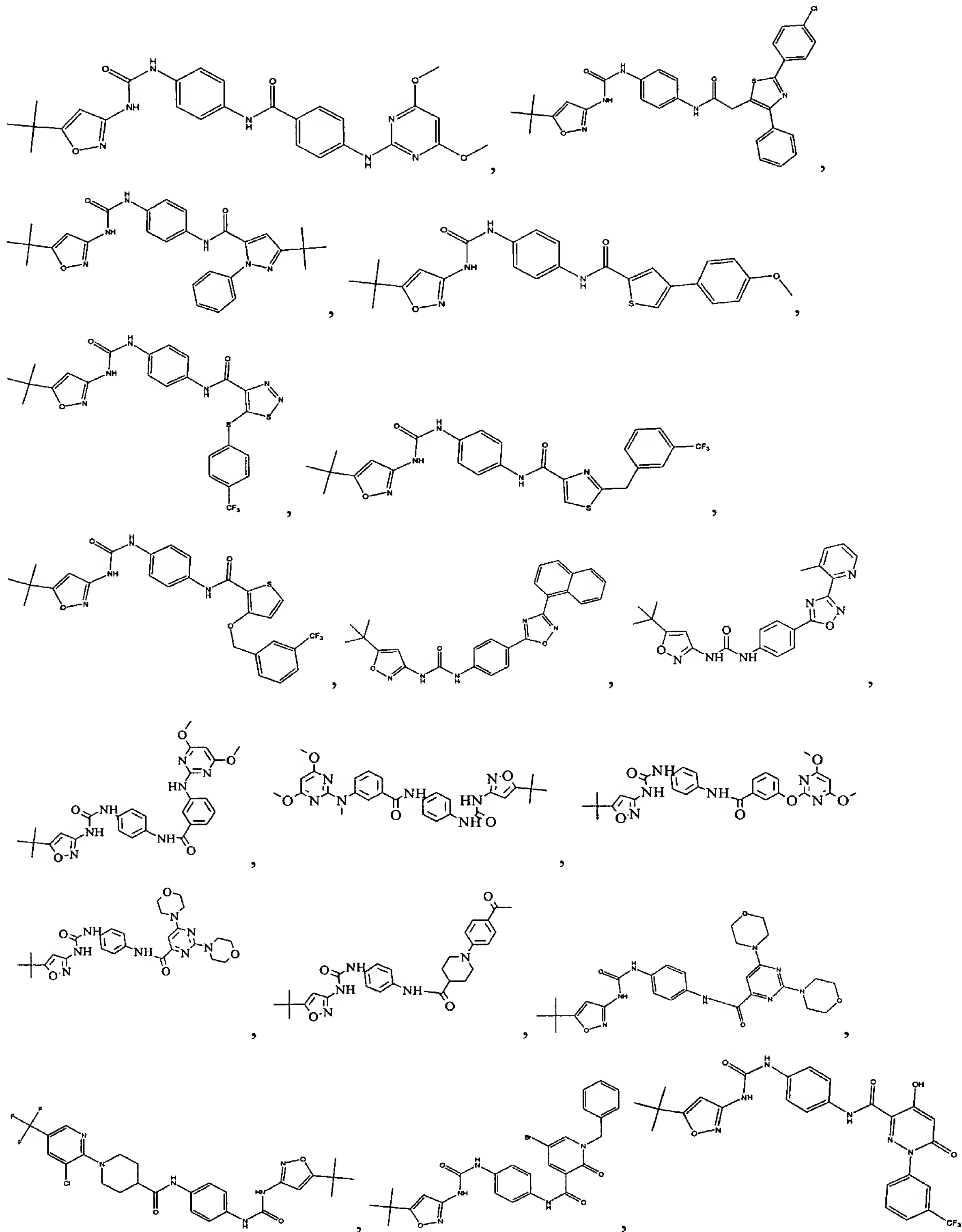
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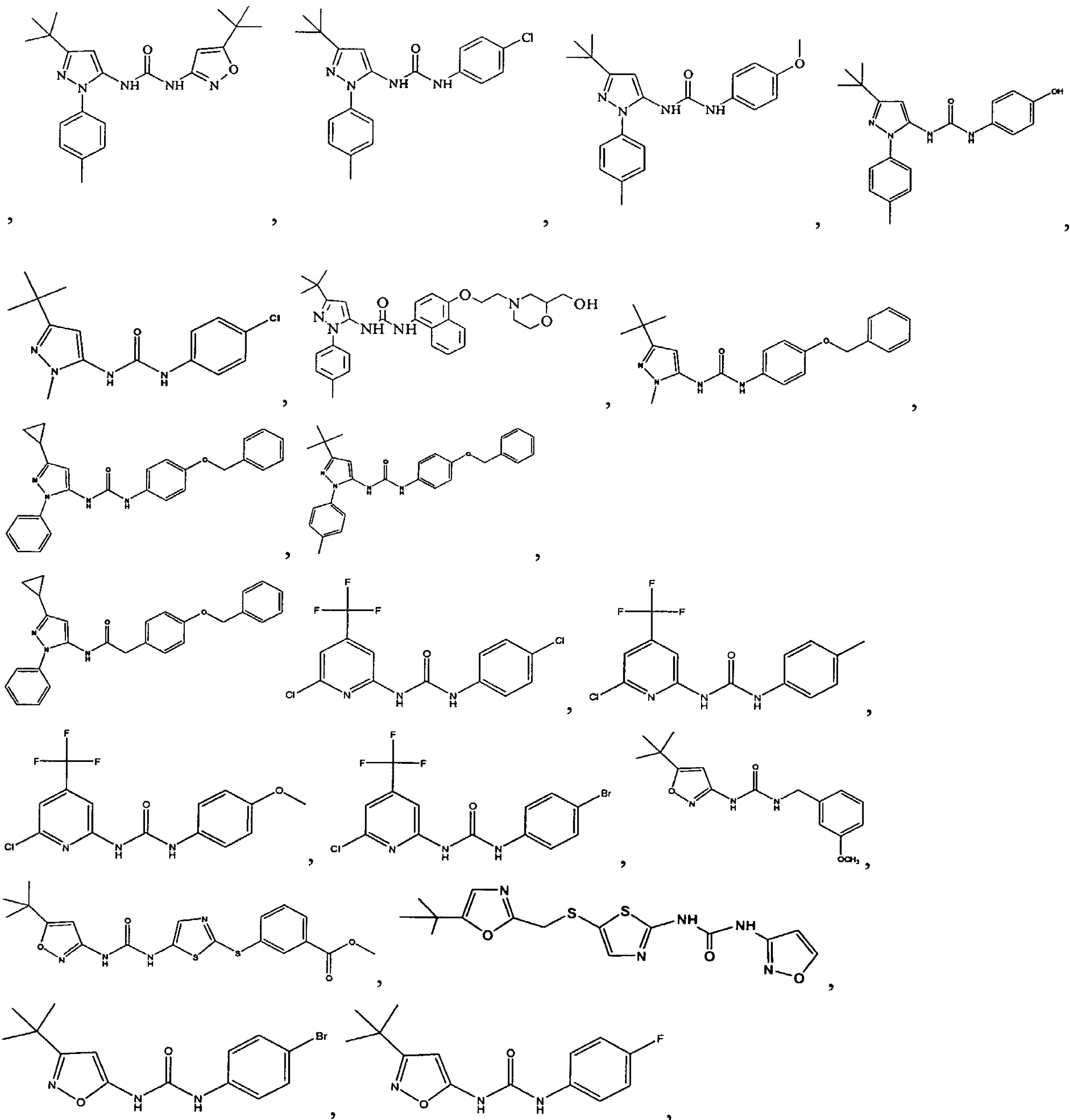


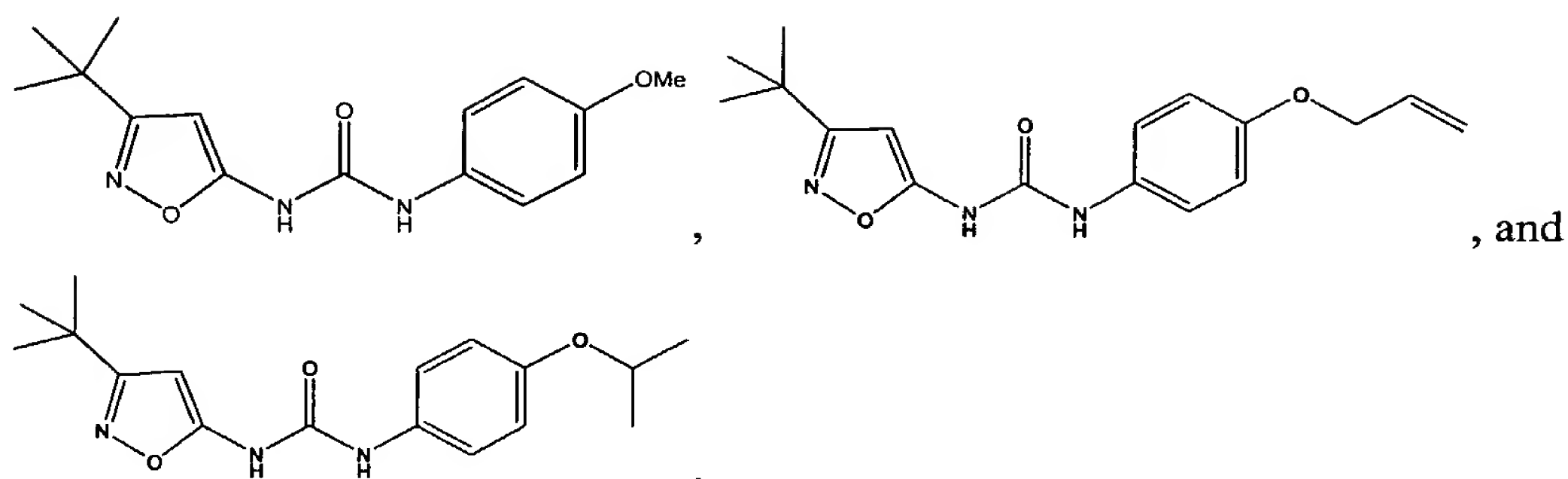
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5



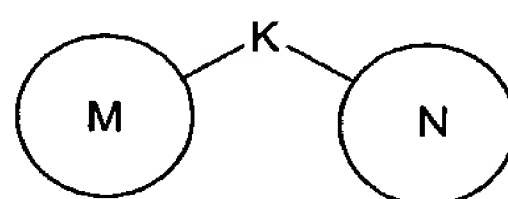






Exemplary ABL Modulators

Methods for modulating abl kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:

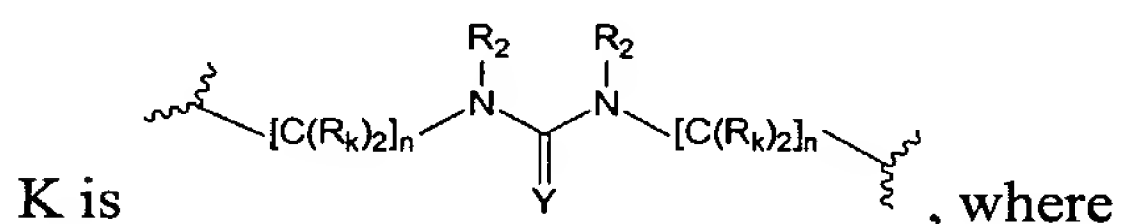


wherein:

M is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

and



Y is O or S;

each R_k is independently H, halogen, substituted or unsubstituted alkyl,

-OH, substituted or unsubstituted alkoxy, -OC(O) R_2 , -NO₂, -N(R_2)₂,

-SR₂, -C(O) R_2 , -C(O)₂ R_2 , -C(O)N(R_2)₂, or -N(R_2)C(O) R_2 ,

each R_2 is independently H, substituted or unsubstituted alkyl, substituted

or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl,

substituted or unsubstituted aryl, or substituted or unsubstituted

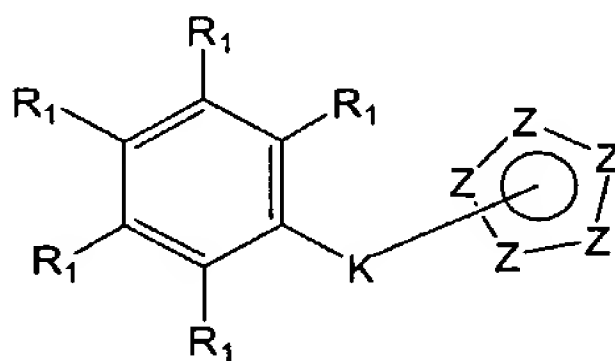
heteroaryl; or wherein two R_2 groups are linked together by an

optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer,
pharmaceutically acceptable salt or solvate thereof.

Methods for modulating abl kinase, said method comprising administering an effective
amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the
5 following structure are provided herein:



wherein:

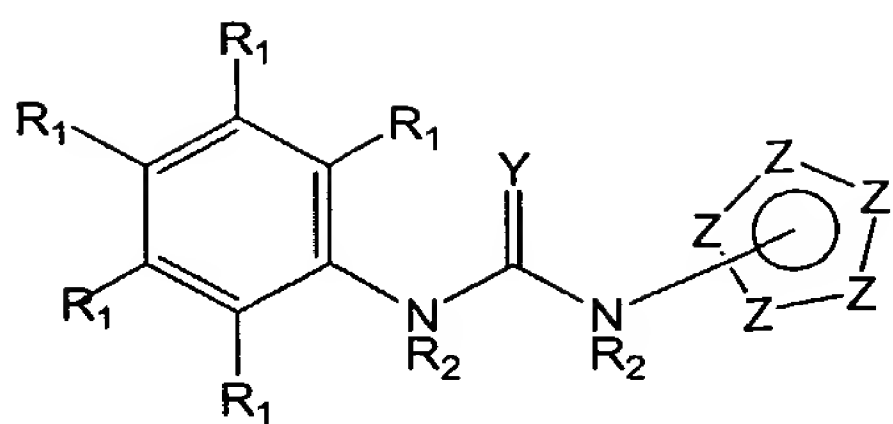
each Z is independently C, CR₃, N, NR₃, O, or S, provided that no more than two
Z's are heteroatoms and wherein no two adjacent Z's are O or S,

10 where R₃ is H, substituted or unsubstituted alkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or
substituted or unsubstituted aryl; and

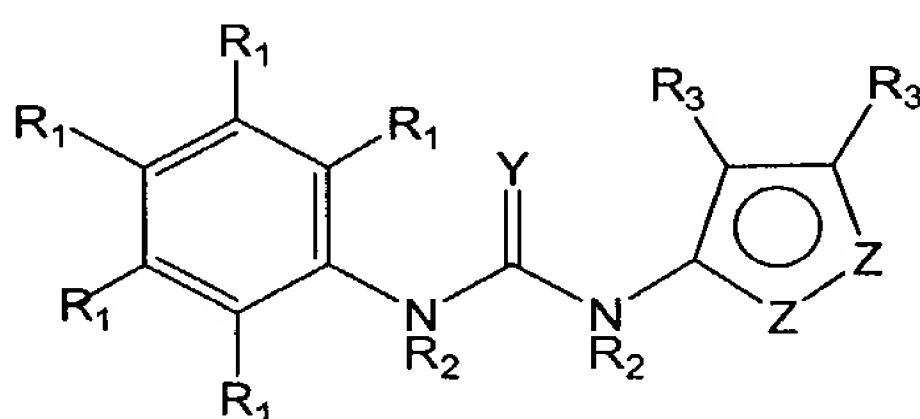
each R₁ is independently H, halogen, substituted or unsubstituted alkyl,
substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl,
15 substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl,
substituted or unsubstituted heteroaryl, -OR_c -OH, -OC(O)R_c, -NO₂, -N(R_c)₂, -
SR_c, S(O)_jR_c where j is 1 or 2, -NR_cC(O)R_c, -C(O)N(R_c)₂, -C(O)₂R_c, or -
C(O)R_c; or two adjacent R₁'s, are taken together to form a substituted or
unsubstituted aryl or heteroaryl,

20 each R_c is independently H, substituted or unsubstituted alkyl, substituted
or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl.

Methods for modulating abl kinase, said method comprising administering an effective
amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the
25 following structure are provided herein:

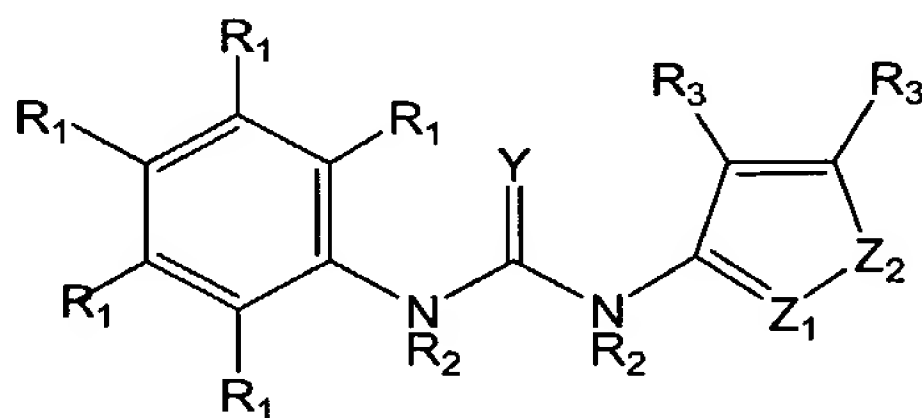


Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



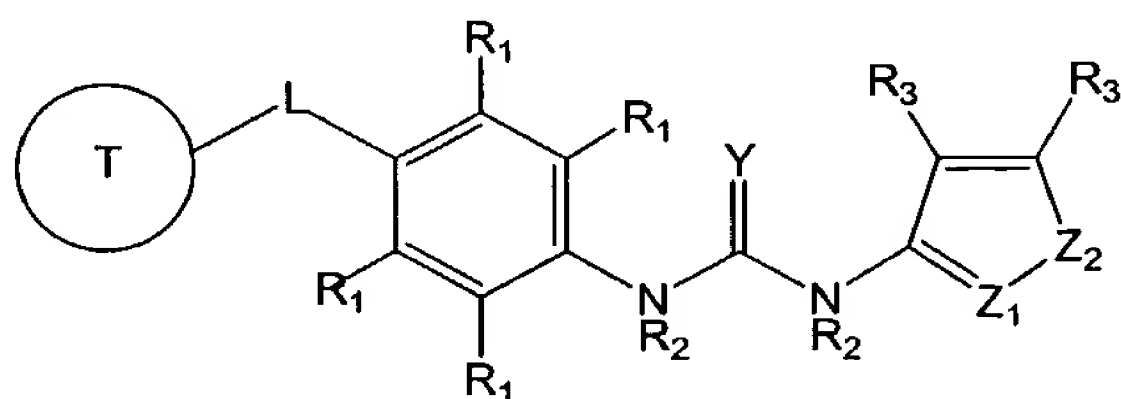
5

Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



10 wherein Z_1 is CR_3 or N; and Z_2 is O or S.

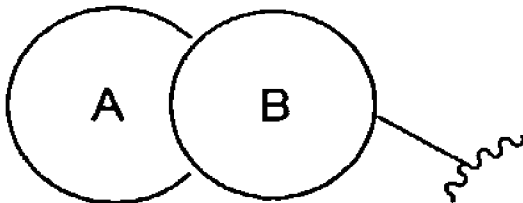
Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



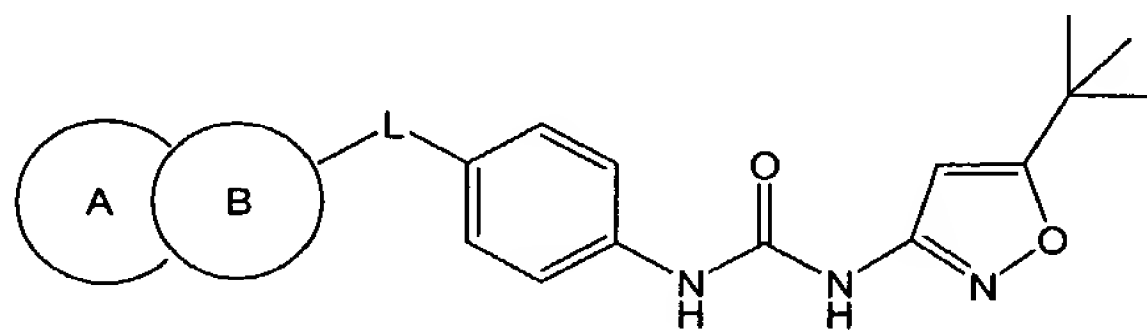
15 wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-C(O)NH-$, $-C(O)-$, $-NH-$, $-O-$, $-S-$, $-O(\text{substituted or unsubstituted alkylene})-$, $-N(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkenylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkenylene})-$, $-C(O)(\text{substituted or unsubstituted alkenylene})-$, and $-NHC(O)(\text{substituted or unsubstituted alkylene})S(\text{substituted or unsubstituted alkylene})C(O)NH-$; and

T is a mono-, bi-, or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

In some embodiments, T is  wherein A is a substituted or unsubstituted five or six-membered heterocyclyl, aryl, or heteroaryl; and B is a substituted or unsubstituted five or six-membered heterocyclene, arylene, or heteroarylene, wherein A and B together form a fused two ring moiety.

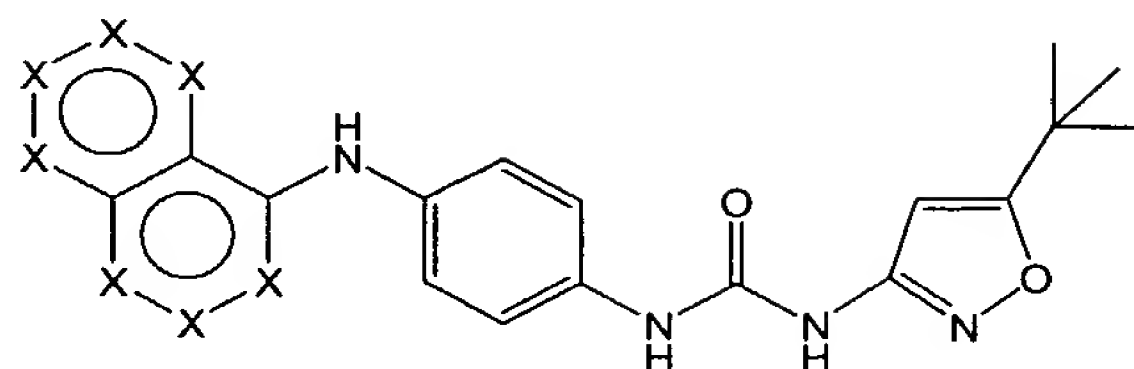
Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



In some embodiments, L of said compound is $-O(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH-$, or a covalent bond. In other embodiments, A of said compound is substituted or unsubstituted five or six-membered aryl or heteroaryl; and B of said compound is substituted or unsubstituted five or six-membered arylene or heteroarylene.

Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the

following structure are provided herein:



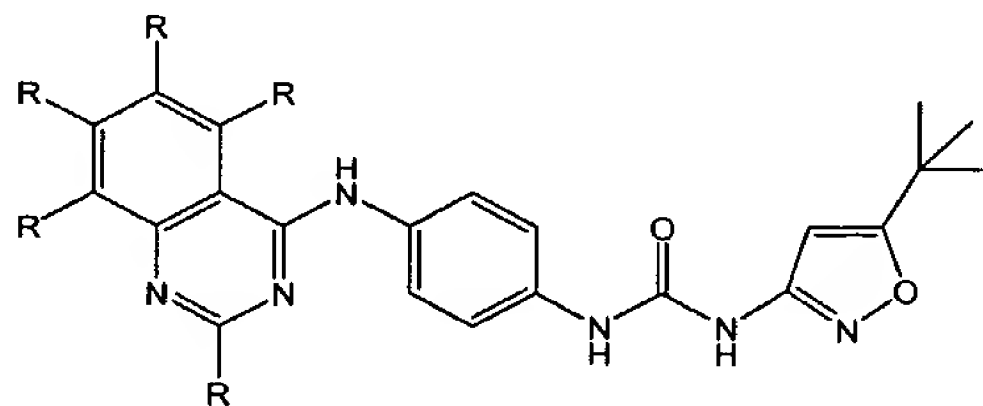
wherein:

each X is independently C, CR, N, NR, or O, wherein no more than three X's is a heteroatom, and no two adjacent ring atoms are O; and

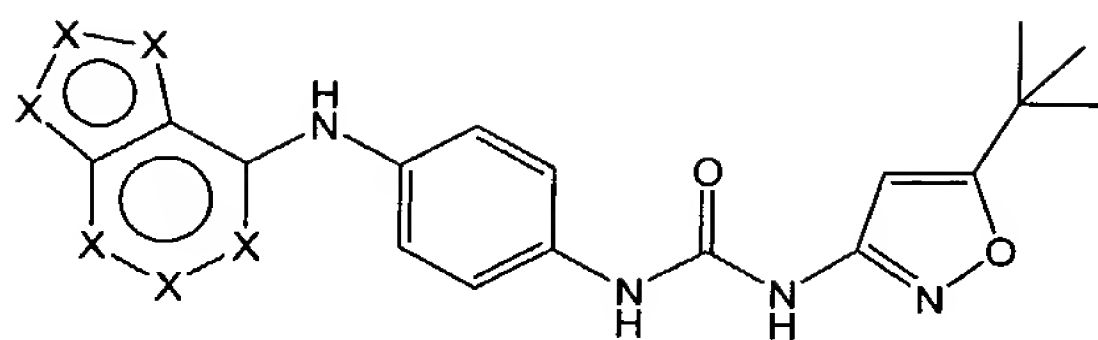
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O)R_d, -NO₂, -N(R_d)₂, -SR_d, -S(O)_jR_d where j is 1 or 2, -NR_d C(O)R_d, -C(O)₂R_d, -C(O)N(R_d)₂ or -C(O)R_d, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



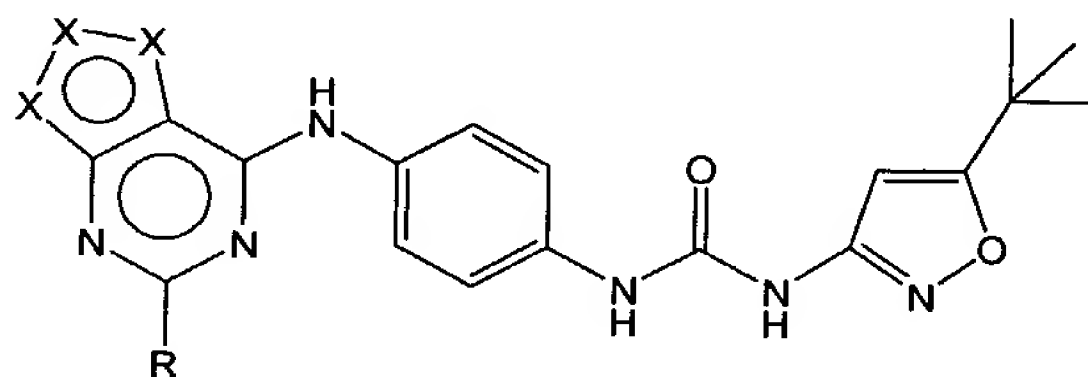
wherein:

each X is independently C, CR, N, NR, or O, wherein no more than three X's is a heteroatom, and no two adjacent ring atoms are O; and

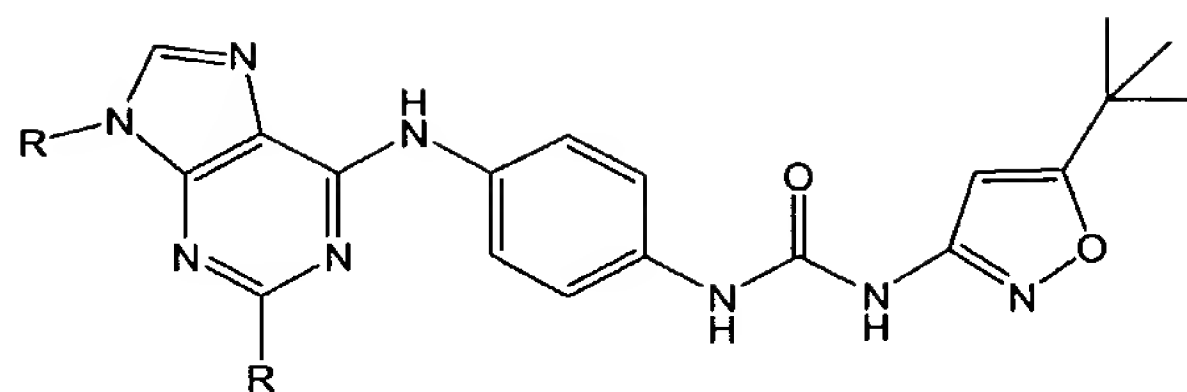
5 each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O)R_d, -NO₂, -N(R_d)₂, -SR_d, -S(O)_jR_d where j is 1 or 2, -NR_d C(O)R_d, -C(O)₂R_d, -C(O)N(R_d)₂ or -C(O)R_d, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

10 each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

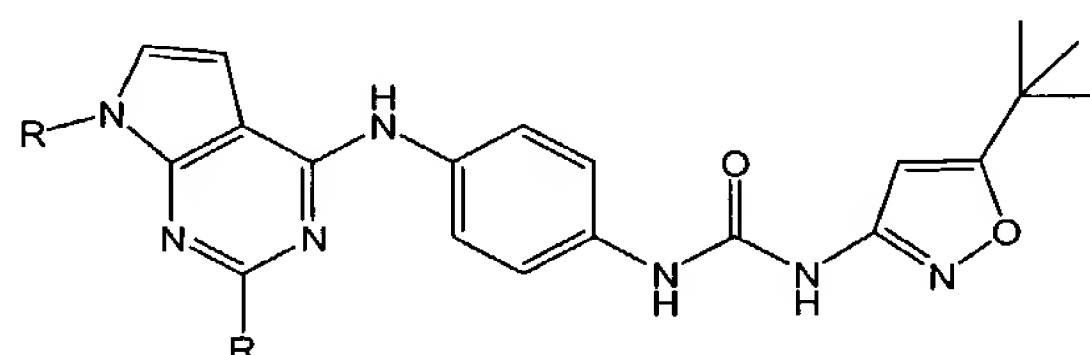
15 Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



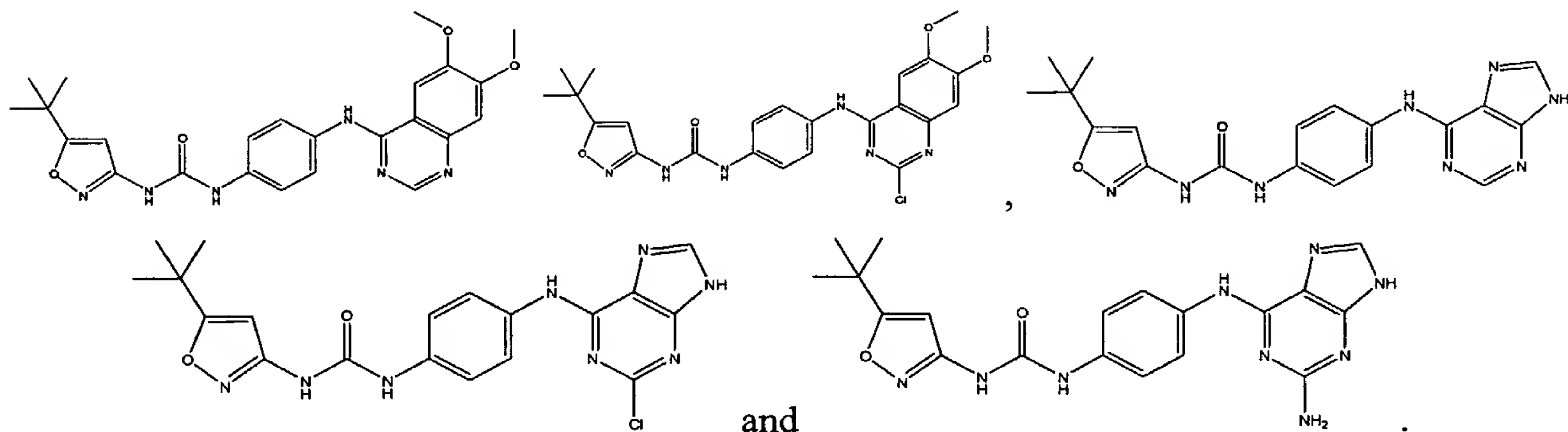
Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



Methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

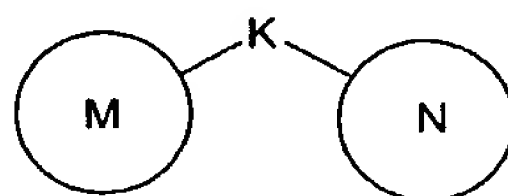


Provided herein are methods for modulating abl kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:



Exemplary PDGFR Modulators

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:

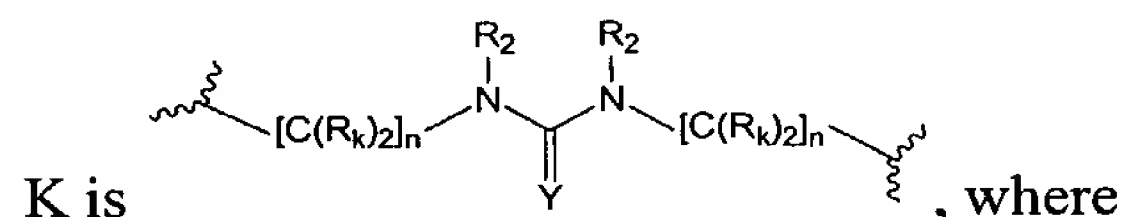


wherein:

M is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

and



Y is O or S;

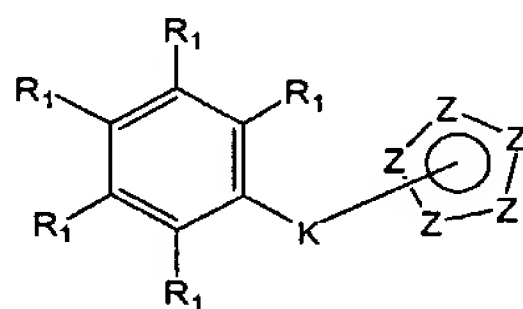
each R_k is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_2 , -NO₂, -N(R_2)₂, -SR₂, -C(O) R_2 , -C(O)₂ R_2 , -C(O)N(R_2)₂, or -N(R_2)C(O) R_2 ,

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein:

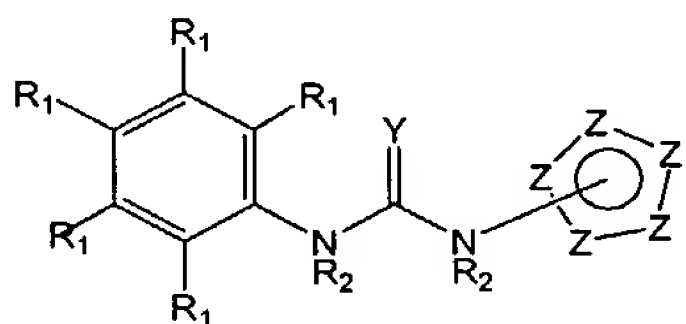
each Z is independently C, CR₃, N, NR₃, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

where R₃ is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

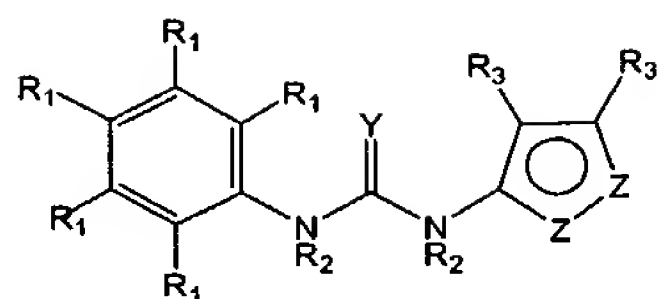
each R₁ is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR_c, -OH, -OC(O)R_c, -NO₂, -N(R_c)₂, -SR_c, S(O)_jR_c where j is 1 or 2, -NR_cC(O)R_c, -C(O)N(R_c)₂, C(O)₂R_c, or -C(O)R_c; or two adjacent R₁'s, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

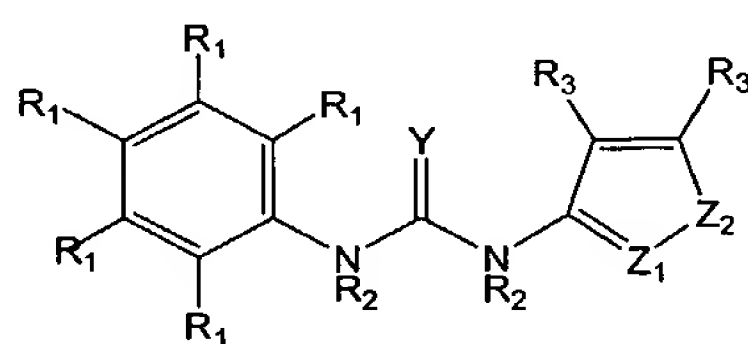
Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

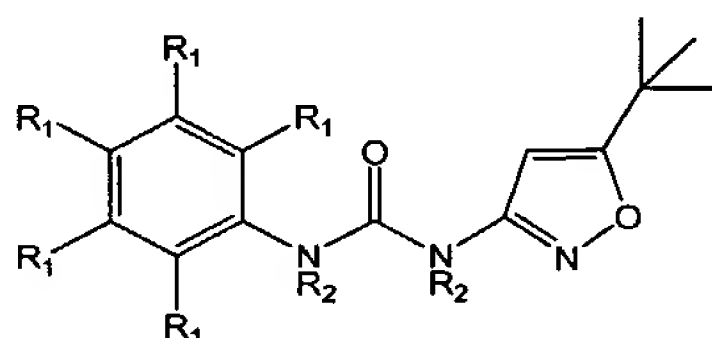


Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein Z_1 is CR_3 or N ; and Z_2 is O or S .

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

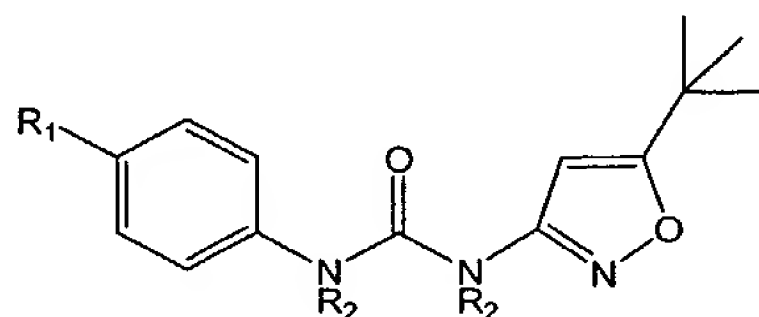


wherein:

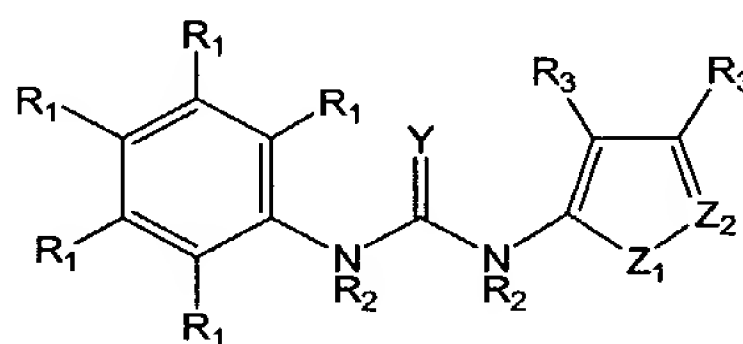
each R_1 is independently H, halogen, substituted or unsubstituted alkyl, -O(substituted or unsubstituted alkyl), -O(substituted or unsubstituted alkenyl), - $NR_cC(O)O$ (substituted or unsubstituted alkyl), - $NR_cC(O)$ (substituted or unsubstituted alkyl), - $NR_cC(O)$ (substituted or unsubstituted alkenyl), - $C(O)NR_c$ (substituted or unsubstituted alkyl), - $C(O)NR_c$ (substituted or unsubstituted alkenyl), - NO_2 , - $S(=O)R_c$, - SR_c , $C(O)_2R_c$, or - $C(O)R_c$; and

each R_2 is independently H or substituted or unsubstituted alkyl.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

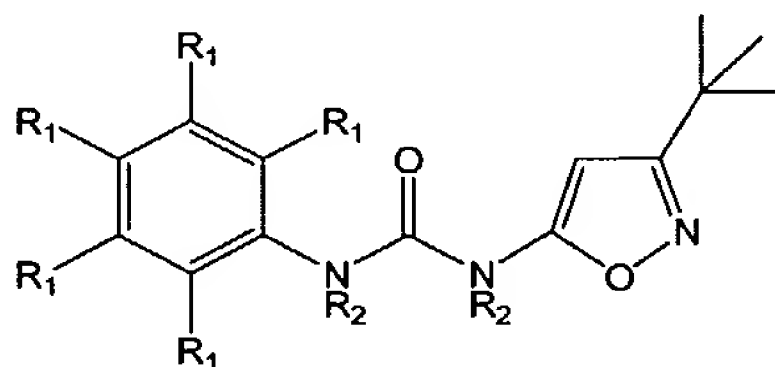


5 Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein Z_1 is O or S; and Z_2 is CR_3 or N.

10 Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



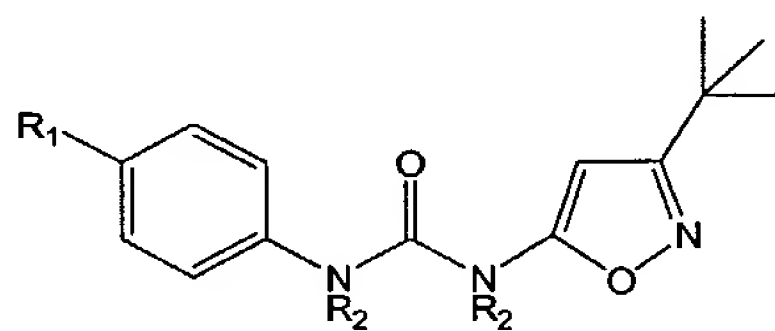
wherein:

15 each R_1 is independently H, halogen, substituted or unsubstituted alkyl, -O(substituted or unsubstituted alkyl), -O(substituted or unsubstituted alkenyl), - $NR_cC(O)O$ (substituted or unsubstituted alkyl), - $NR_cC(O)$ (substituted or unsubstituted alkyl), - $NR_cC(O)$ (substituted or unsubstituted

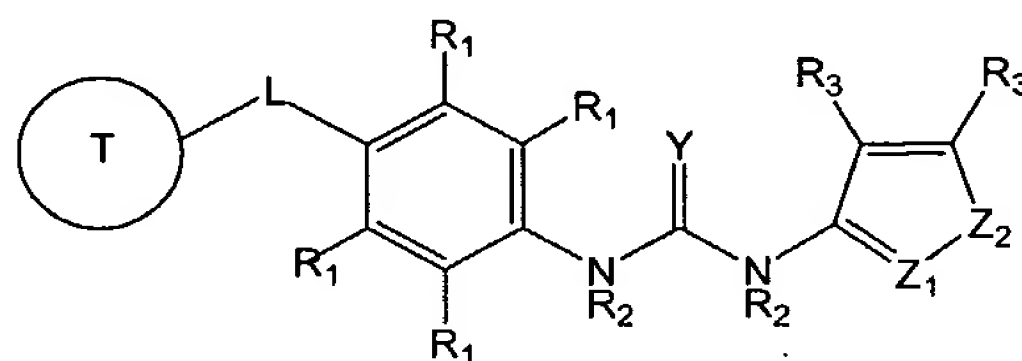
alkenyl), $-\text{C}(\text{O})\text{NR}_c$ (substituted or unsubstituted alkyl), $-\text{C}(\text{O})\text{NR}_c$ (substituted or unsubstituted alkenyl), $-\text{NO}_2$, $-\text{S}(=\text{O})\text{R}_c$, $-\text{SR}_c$, $\text{C}(\text{O})_2\text{R}_c$, or $-\text{C}(\text{O})\text{R}_c$; and

each R_2 is independently H or substituted or unsubstituted alkyl, or two R_2 groups are linked together to form an optionally substituted alkylene.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

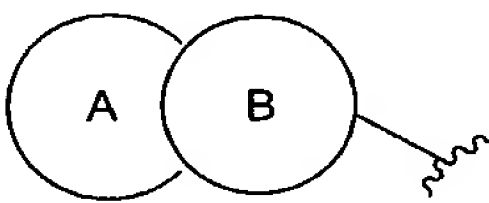


wherein:

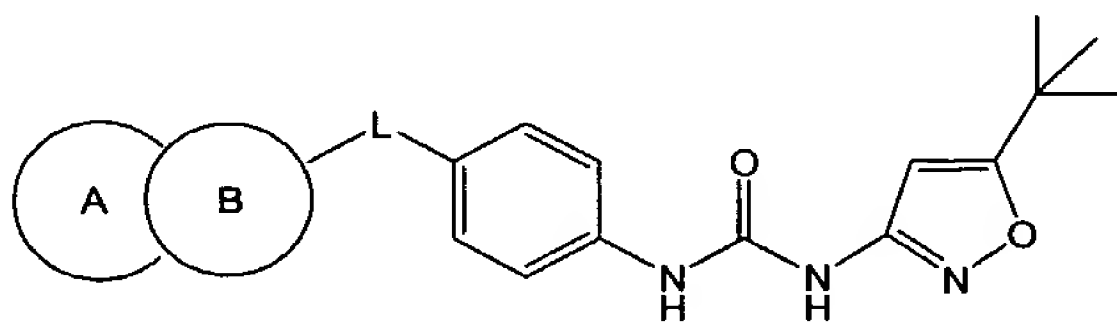
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{O}(\text{substituted or unsubstituted alkylene})-$, $-\text{N}(\text{substituted or unsubstituted alkylene})-$, $-\text{C}(\text{O})\text{NH}(\text{substituted or unsubstituted alkylene})-$, $-\text{C}(\text{O})\text{NH}(\text{substituted or unsubstituted alkenylene})-$, $-\text{NHC}(\text{O})(\text{substituted or unsubstituted alkylene})-$, $-\text{NHC}(\text{O})(\text{substituted or unsubstituted alkenylene})-$, $-\text{C}(\text{O})(\text{substituted or unsubstituted alkenylene})-$,

and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

T is a mono-, bi-, or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

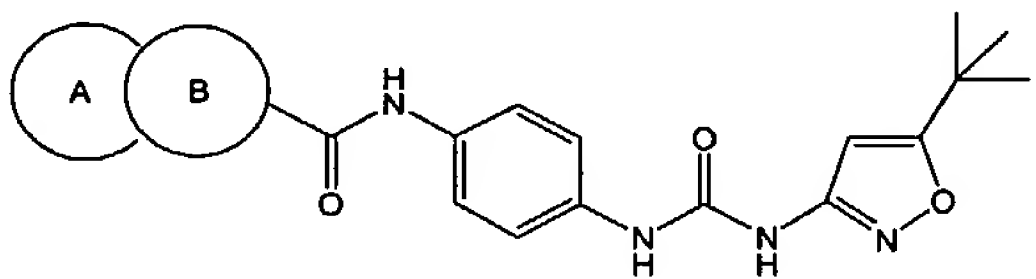
- 5 In some embodiments, T is  wherein A is a substituted or unsubstituted five or six-membered heterocyclyl, aryl, or heteroaryl; and B is a substituted or unsubstituted five or six-membered heterocyclene, arylene, or heteroarylene, wherein A and B together form a fused two ring moiety.

- 10 Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



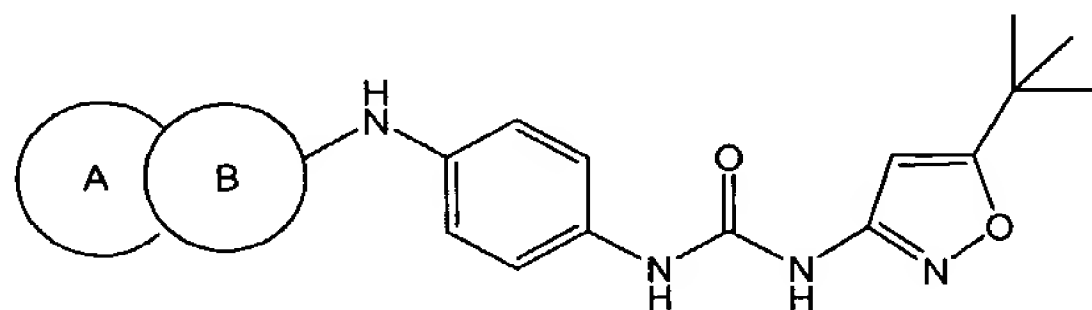
- 15 In some embodiments, L of said compound is a covalent bond, --C(O)NH(substituted or unsubstituted alkylene), -NHC(O)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NH-, or -O(substituted or unsubstituted alkylene)-.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



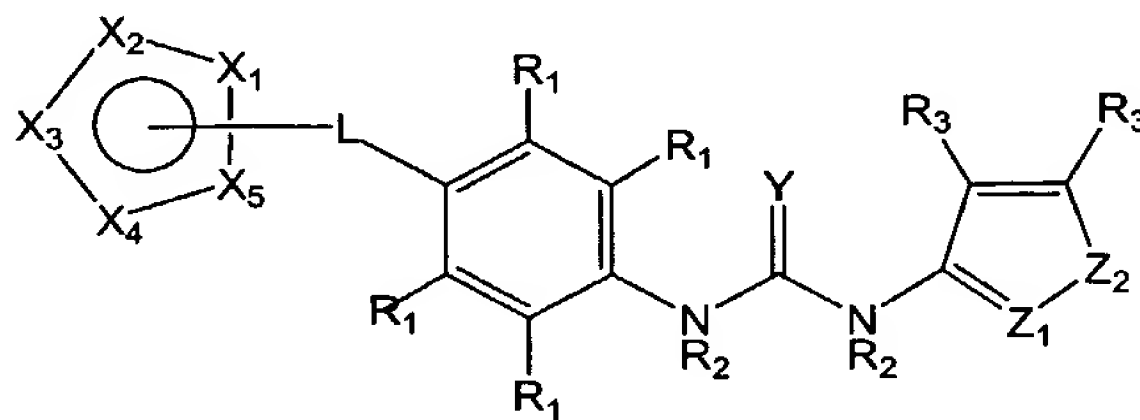
In some embodiments, B of said compound is a substituted or unsubstituted five-membered heteroarylene. In other embodiments, said five-membered heteroarylene is substituted or unsubstituted thiophenylene. In still other embodiments, B is substituted or unsubstituted imidazolylene. In yet other embodiments, B is substituted or unsubstituted pyrrolylene. In other embodiments, B of said compound is a substituted or unsubstituted 6-membered arylene or heteroarylene. In still other embodiments, B is substituted or unsubstituted phenylene. In some embodiments, B is substituted or unsubstituted pyridinylenes or isopyridazine.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



In some embodiments, B of said compound is a substituted or unsubstituted six-membered heteroarylene. In other embodiments, six-membered heteroarylene is substituted or unsubstituted pyrimidinylene. In yet other embodiments, L of said compound $-OCH_2-$.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein:

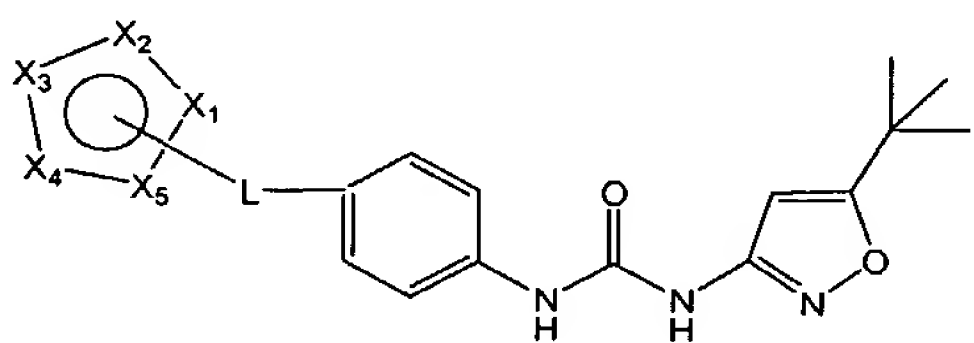
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, -C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

each of X_1 - X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1 - X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where

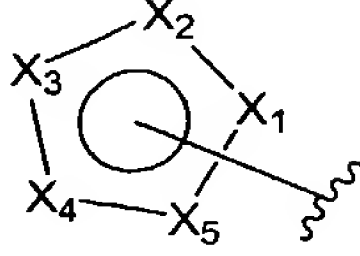
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -S(O)_j R_d where j is 1 or 2, -NR_d C(O) R_d , -C(O)₂ R_d , -C(O)N(R_d)₂ or -C(O) R_d , or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

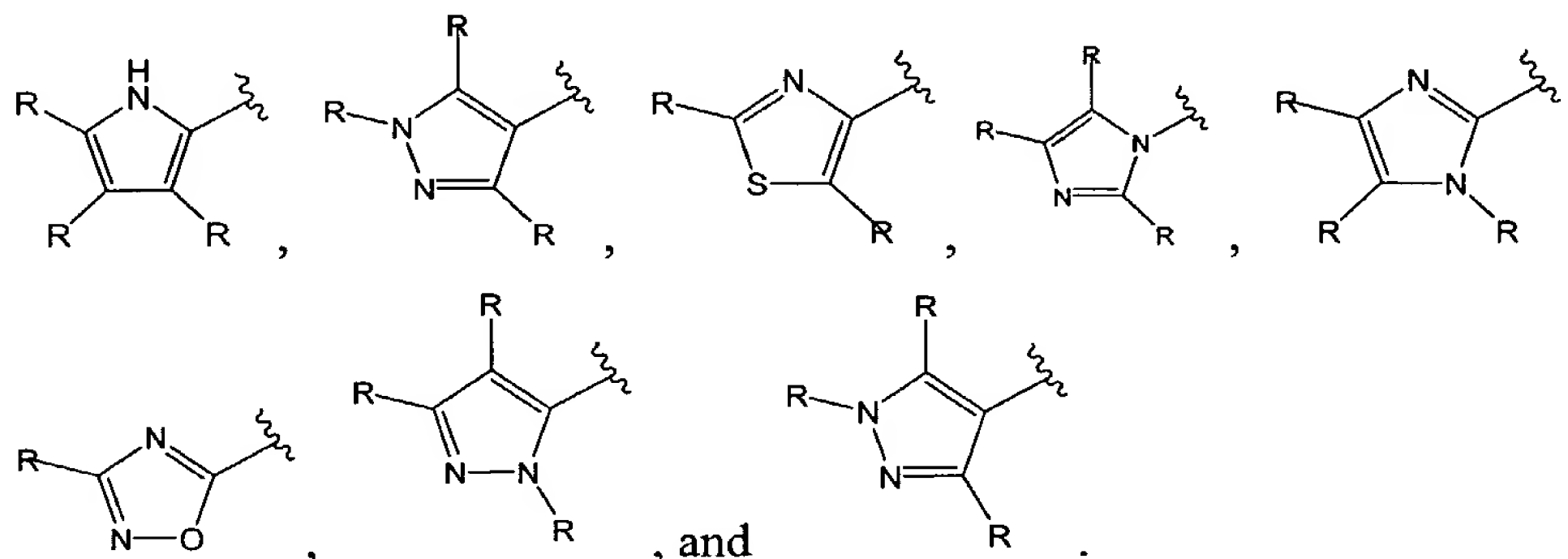
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

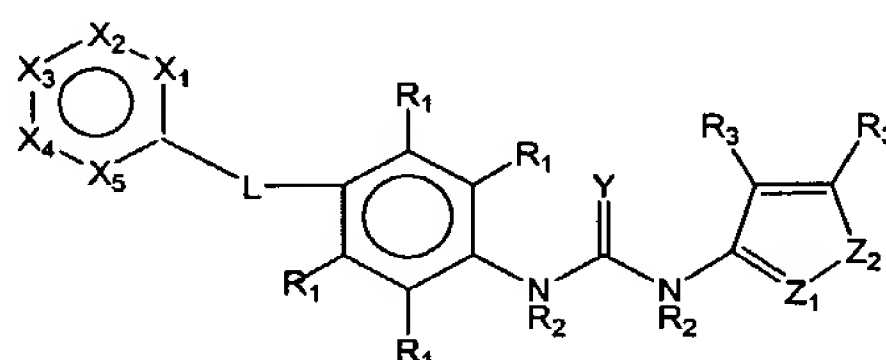


In some embodiments, L of said compound is a covalent bond, -C(O)NH-, or -O(substituted

or unsubstituted alkenylene)-. In other embodiments,  of said compound is selected from the group consisting of:



Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



10 wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, -C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-,

15

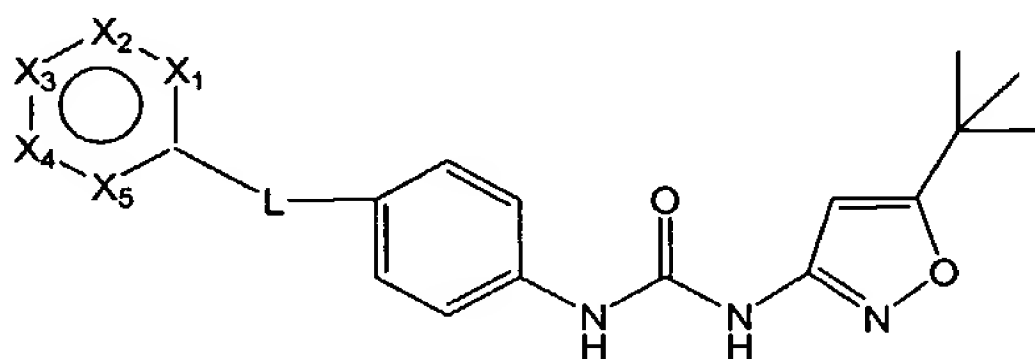
and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

each of X_1 - X_5 is independently C, CR, N-O, or N, wherein no more than two of X_1 - X_5 is N, where

5 each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -S(O)_j R_d where j is 1 or 2, -NR_d C(O) R_d , -C(O)₂ R_d , -C(O)N(R_d)₂ or -C(O) R_d , or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

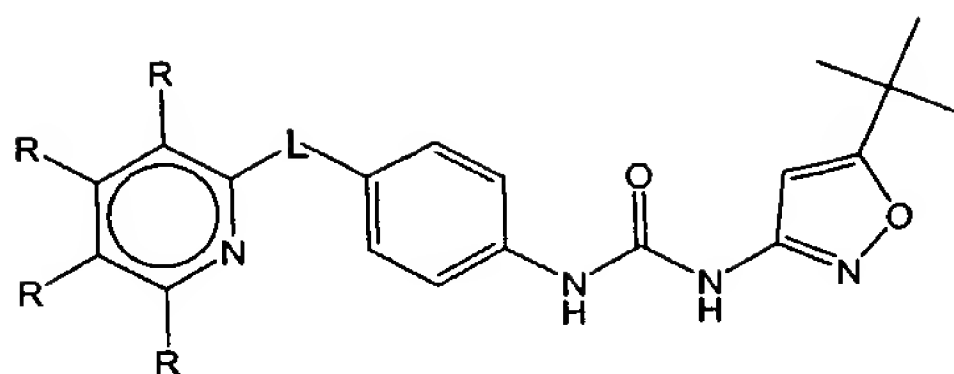
10 each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

15 Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

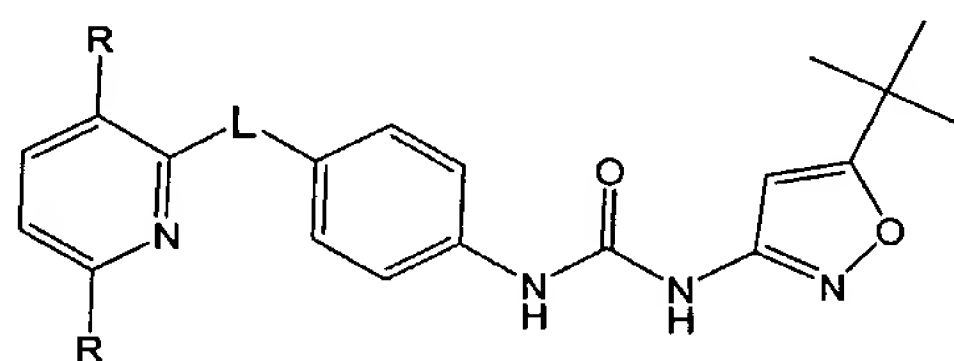


20 In some embodiments, L is a linker selected from the group consisting of a covalent bond, - (substituted or unsubstituted alkylene)-, -NHC(O)-, -C(O)NH(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, and - O(substituted or unsubstituted alkylene)-,

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

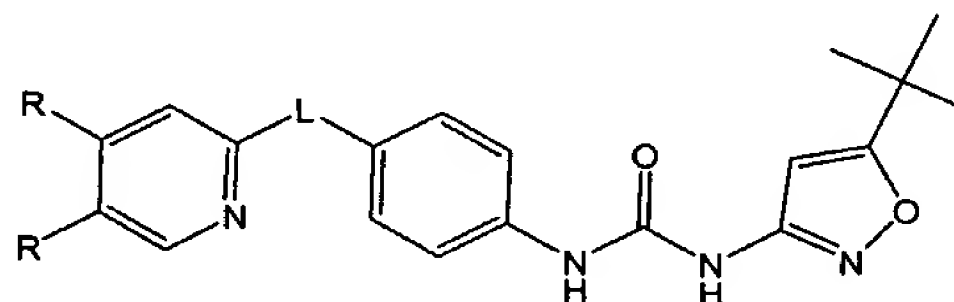


Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



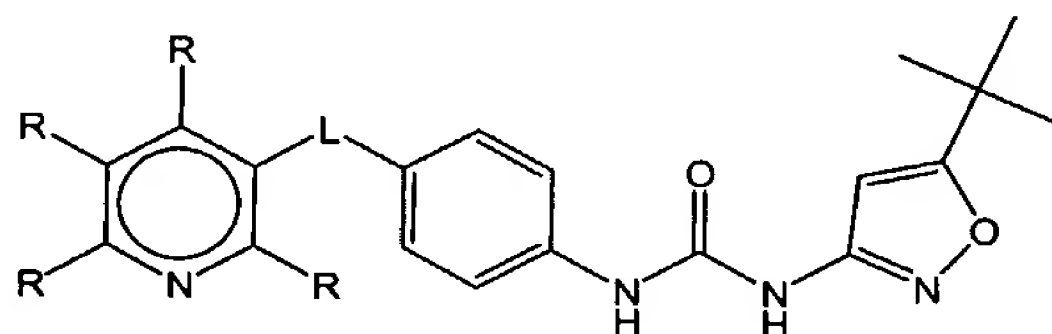
5

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



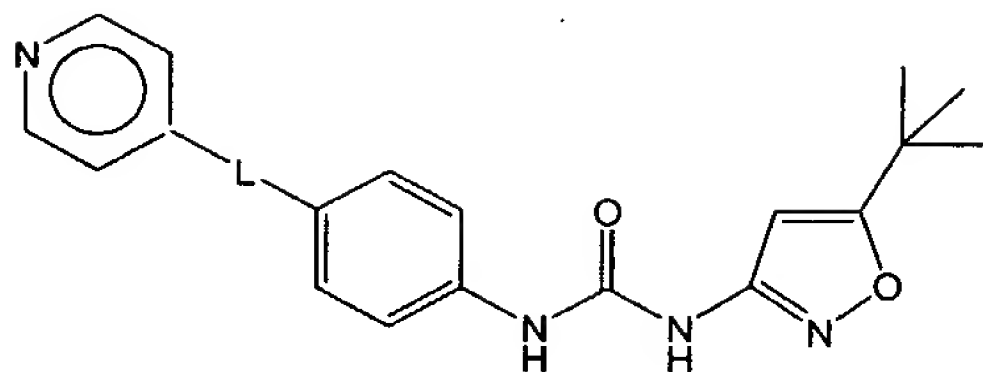
10

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

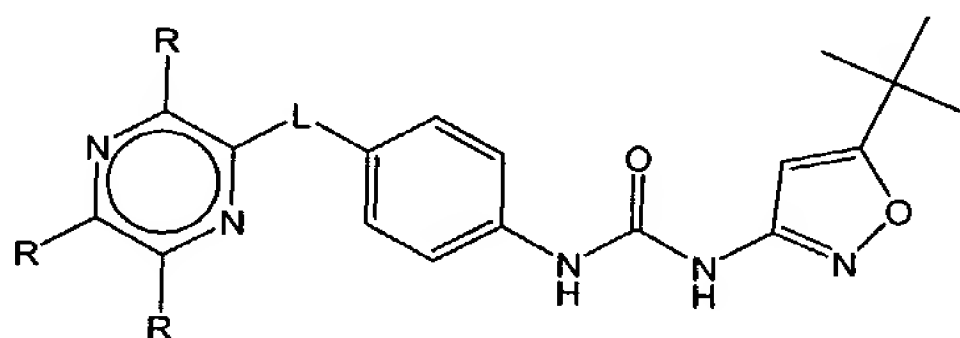


15

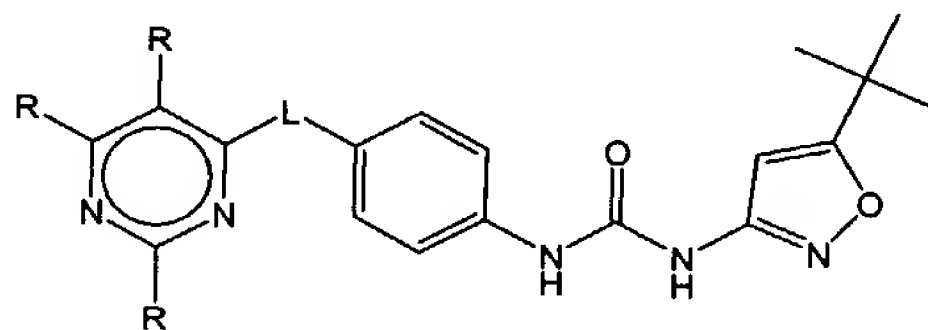
Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



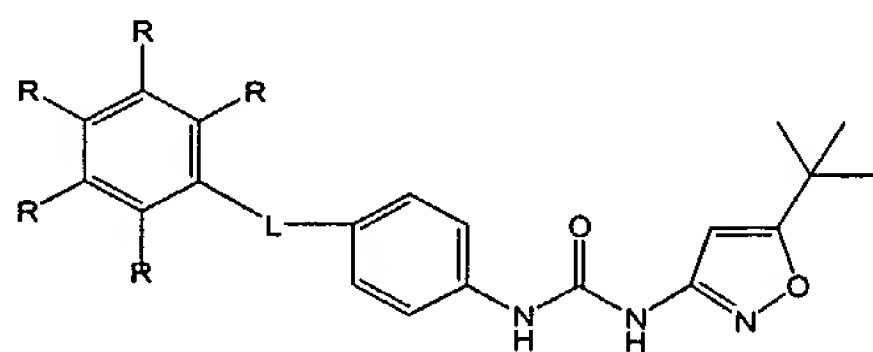
Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



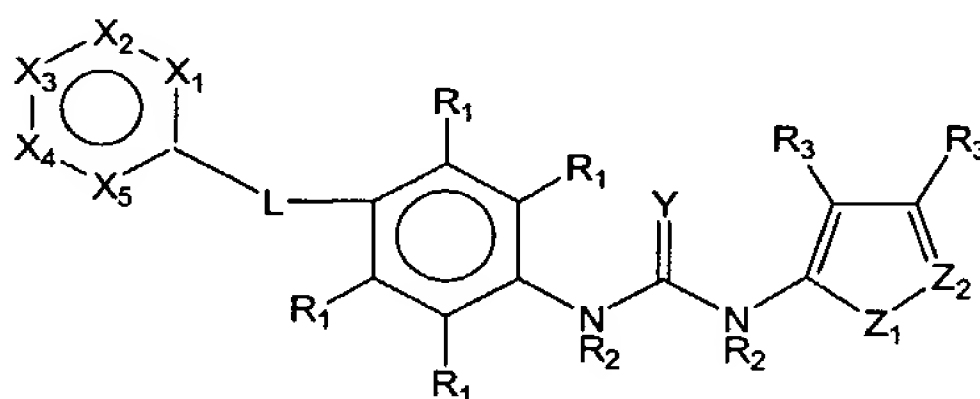
Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



In some embodiments, L of said compound is $-\text{OCH}_2-$ or $-\text{OCH}_2\text{CHCH}_2-$. In other embodiments, L of said compound is $-\text{NHC(O)}-$. In yet other embodiments, L of said compound is a covalent bond, substituted or unsubstituted alkylene, $-\text{NHC(O)}$ (substituted or

unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene), -
C(O)NH(substituted or unsubstituted alkenylene), or -NHC(O)(substituted or unsubstituted
alkenylene)-.

Methods for modulating PDGF-R kinase, said method comprising administering an
effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding
to the following structure are provided herein:



wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or
unsubstituted alkenylene, substituted or unsubstituted alkylene, -C(O)NH-,
-C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -
N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or
unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-,
-NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or
unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-,
and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or
unsubstituted alkylene)C(O)NH-; and

each of X₁-X₅ is independently C, CR, NR, O, S, or N, wherein no more than two
of X₁-X₅ is a hetroatom, and no two adjacent ring atoms are O or S, where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH,
substituted or unsubstituted alkoxy, -OC(O)R_d, -NO₂, -N(R_d)₂, -SR_d, -S(O)_jR_d
where j is 1 or 2, -NR_d C(O)R_d, -C(O)₂R_d, -C(O)N(R_d)₂ or -C(O)R_d, or two
adjacent R's are taken together to form a substituted or unsubstituted aryl or
hetroaryl, where

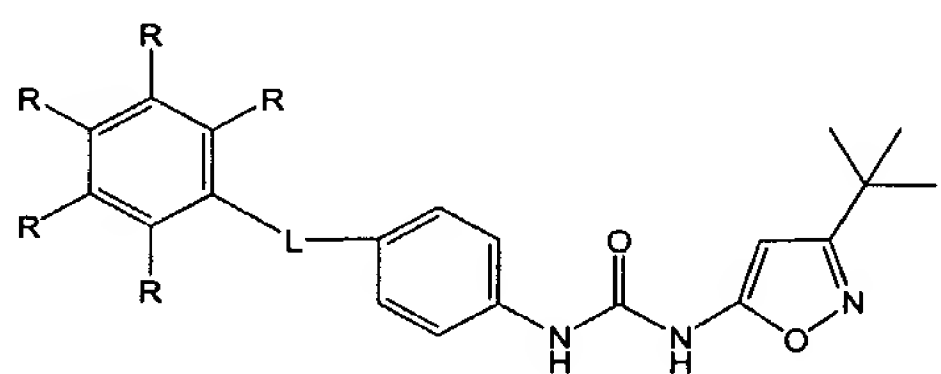
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

Z_1 is O or S; and

5

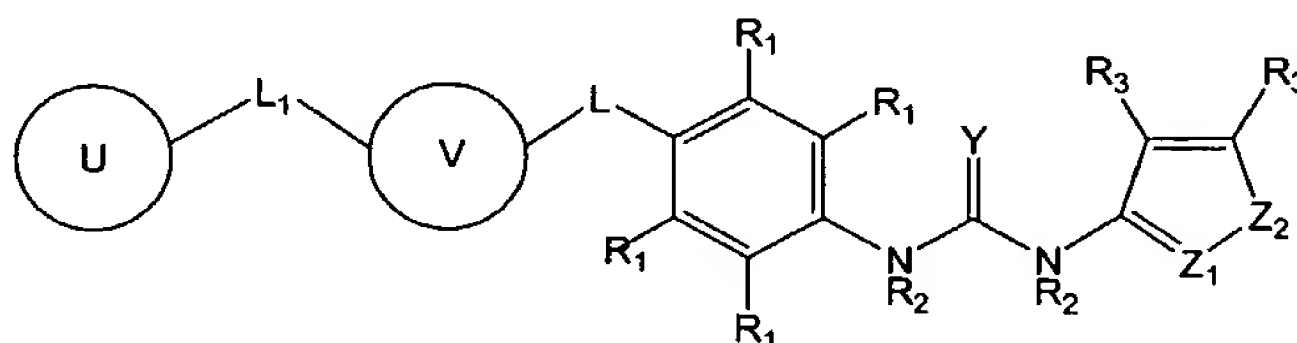
Z_2 is CR_3 or N.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



10

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein:

15

each of L and L_1 is independently a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-C(O)NH-$, $-C(O)-$, $-NH-$, $-O-$, $-S-$, $-O$ (substituted or unsubstituted alkylene)-, $-N$ (substituted or unsubstituted alkylene)-, $-C(O)NH$ (substituted or unsubstituted alkylene), $-C(O)NH$ (substituted or unsubstituted alkenylene)-, $-NHC(O)$ (substituted or unsubstituted alkylene)-, $-NHC(O)$ (substituted or unsubstituted alkenylene)-, $-C(O)$ (substituted or

20

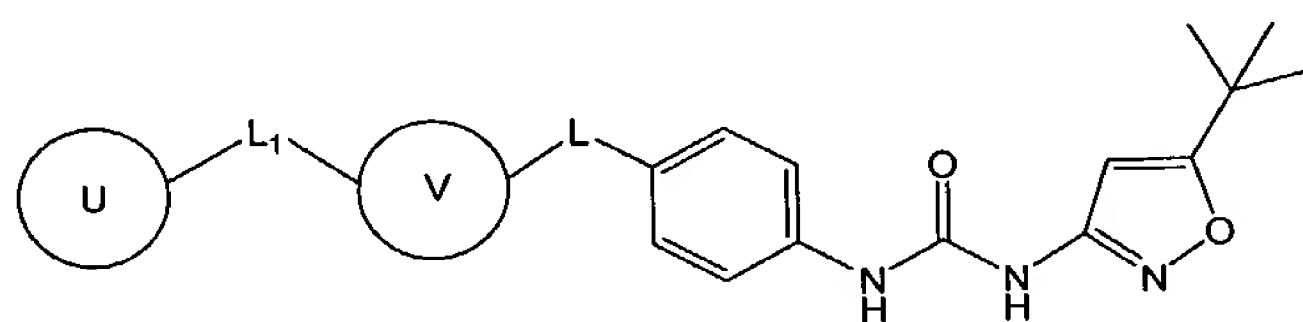
unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-;

U is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

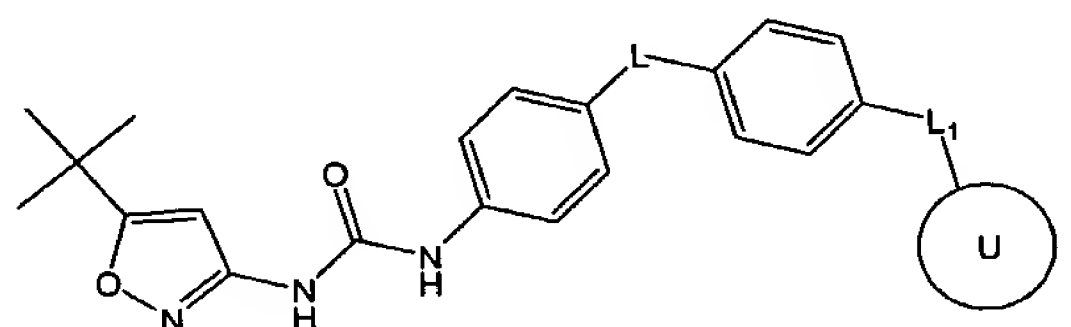
5 V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

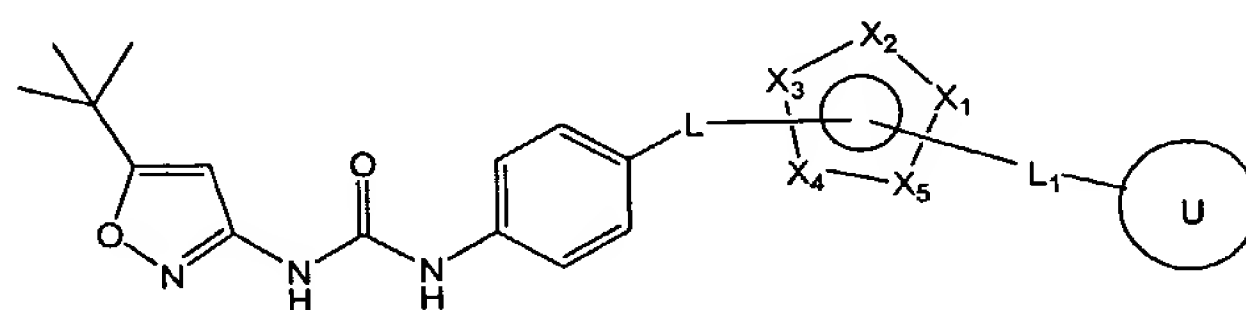
10



Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



15 Methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein:

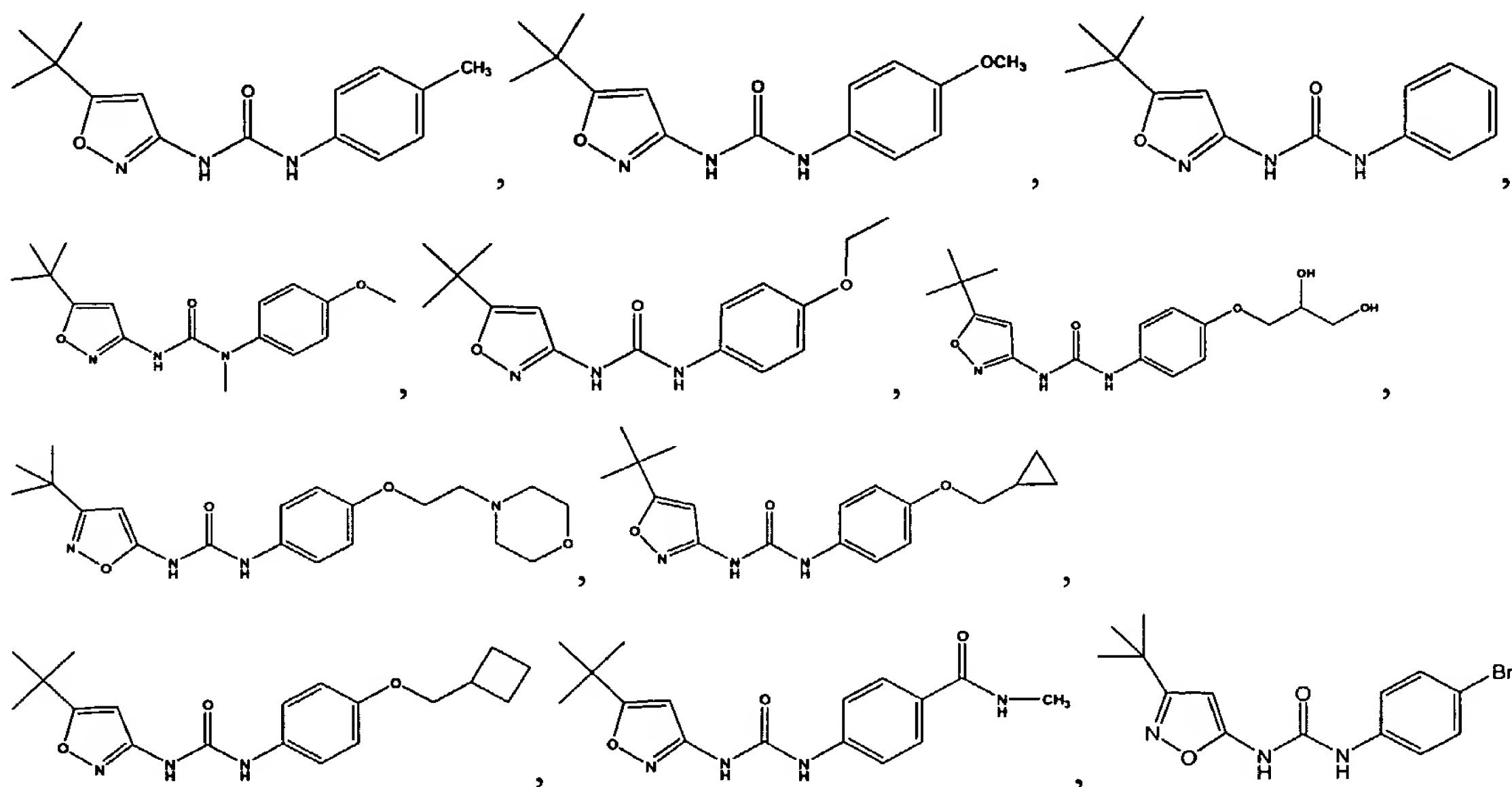
each of X_1 - X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1 - X_5 is a heteroatom, and no two adjacent ring atoms are S or O; and

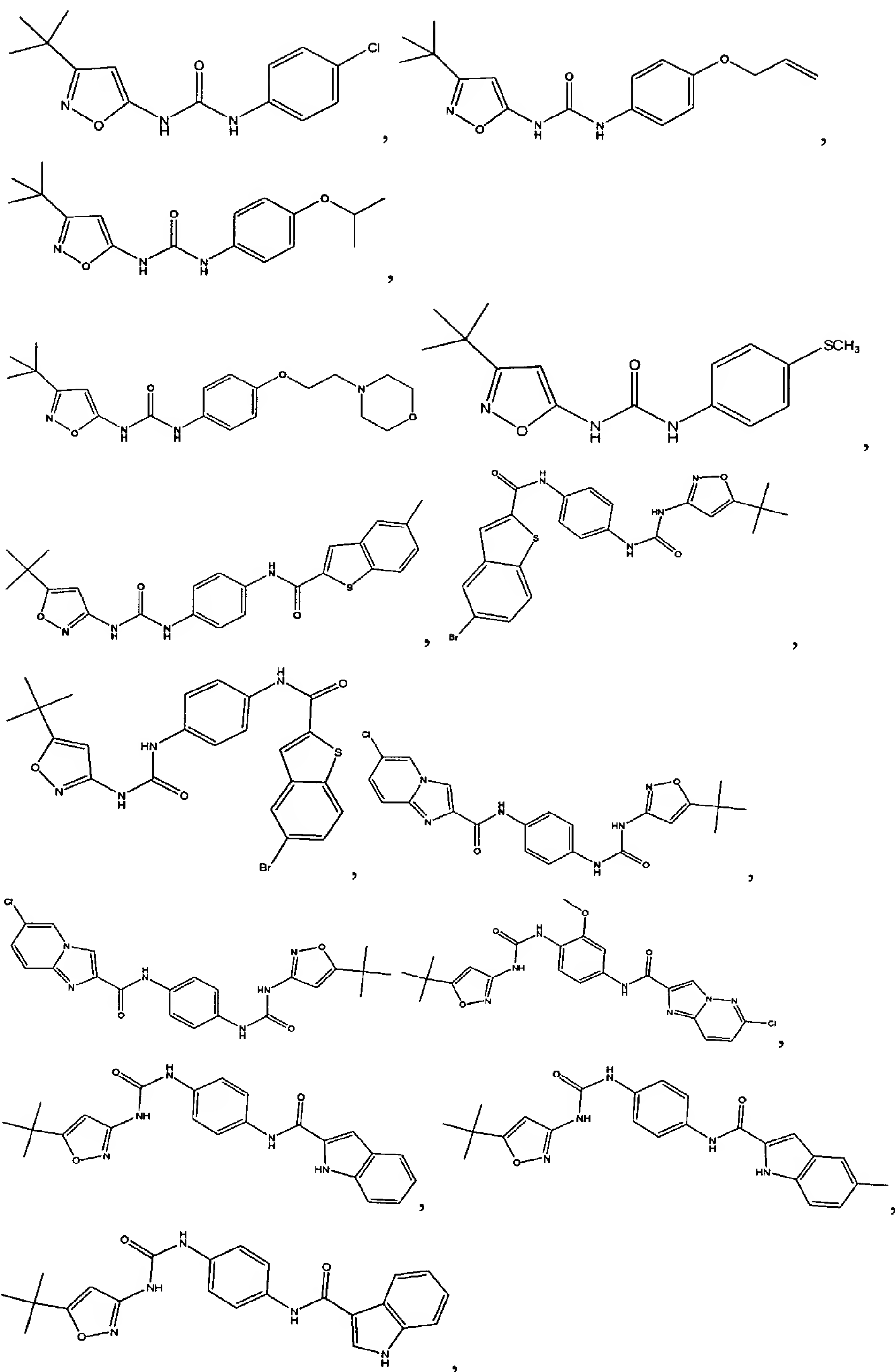
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -S(O)_j R_d where j is 1 or 2, -NR_d C(O) R_d , -C(O)₂ R_d , -C(O)N(R_d)₂ or -C(O) R_d , or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

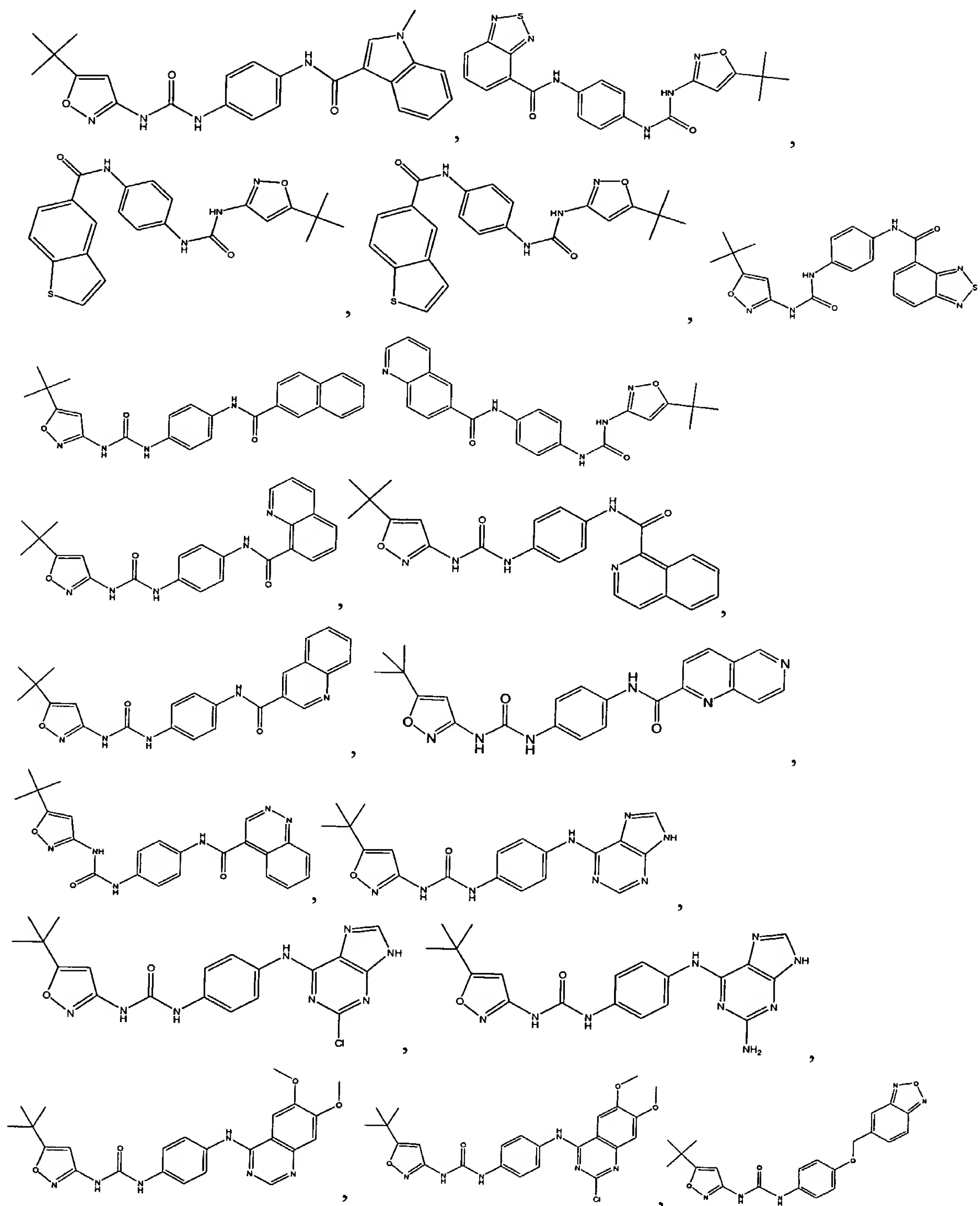
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

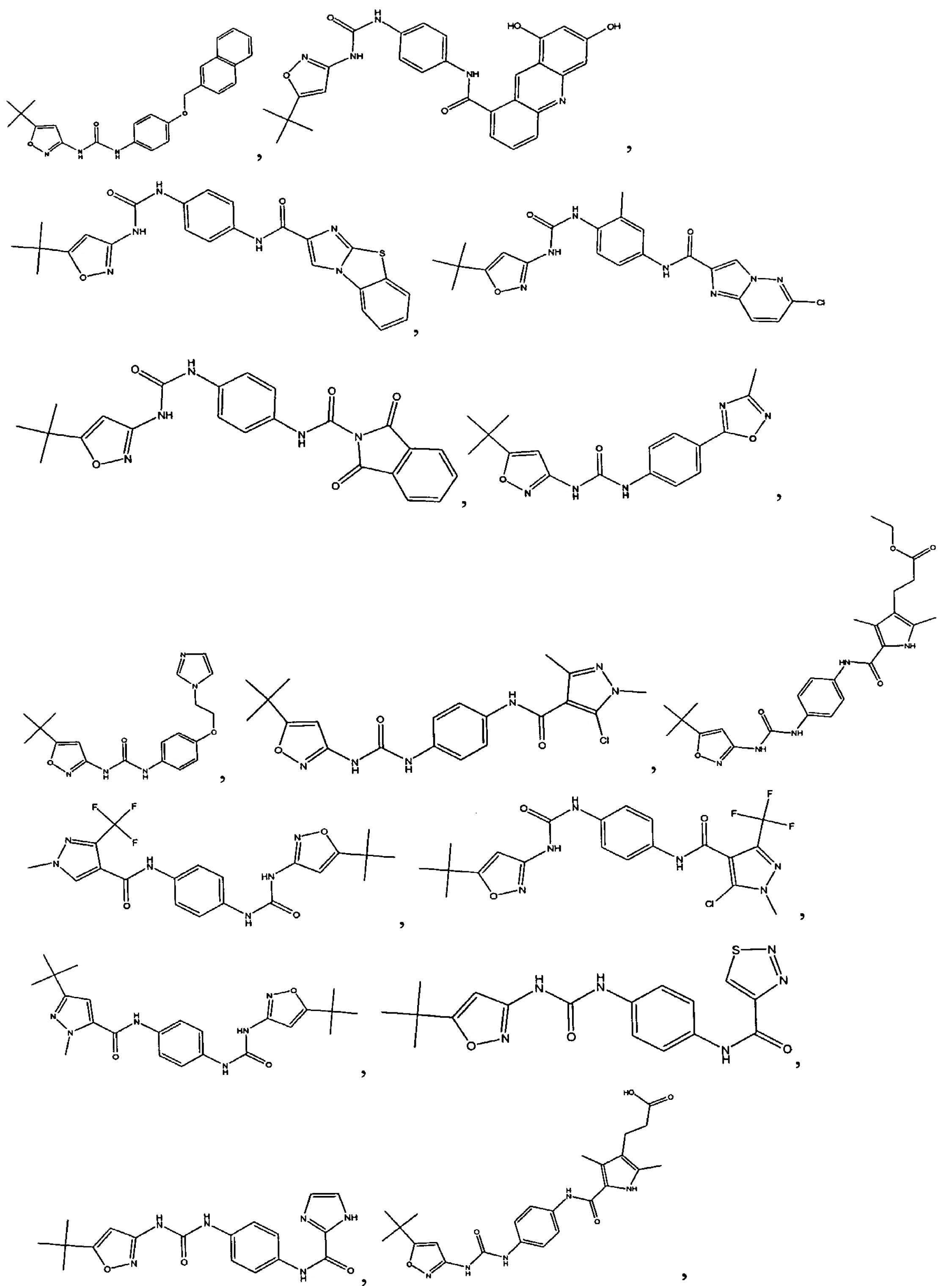
In some embodiments, V is a five-membered hetroarylene group. In other embodiments, U is a substituted or unsubstituted five-membered heteroaryl, substituted or unsubstituted phenyl, or substituted or unsubstituted six-membered heteroaryl.

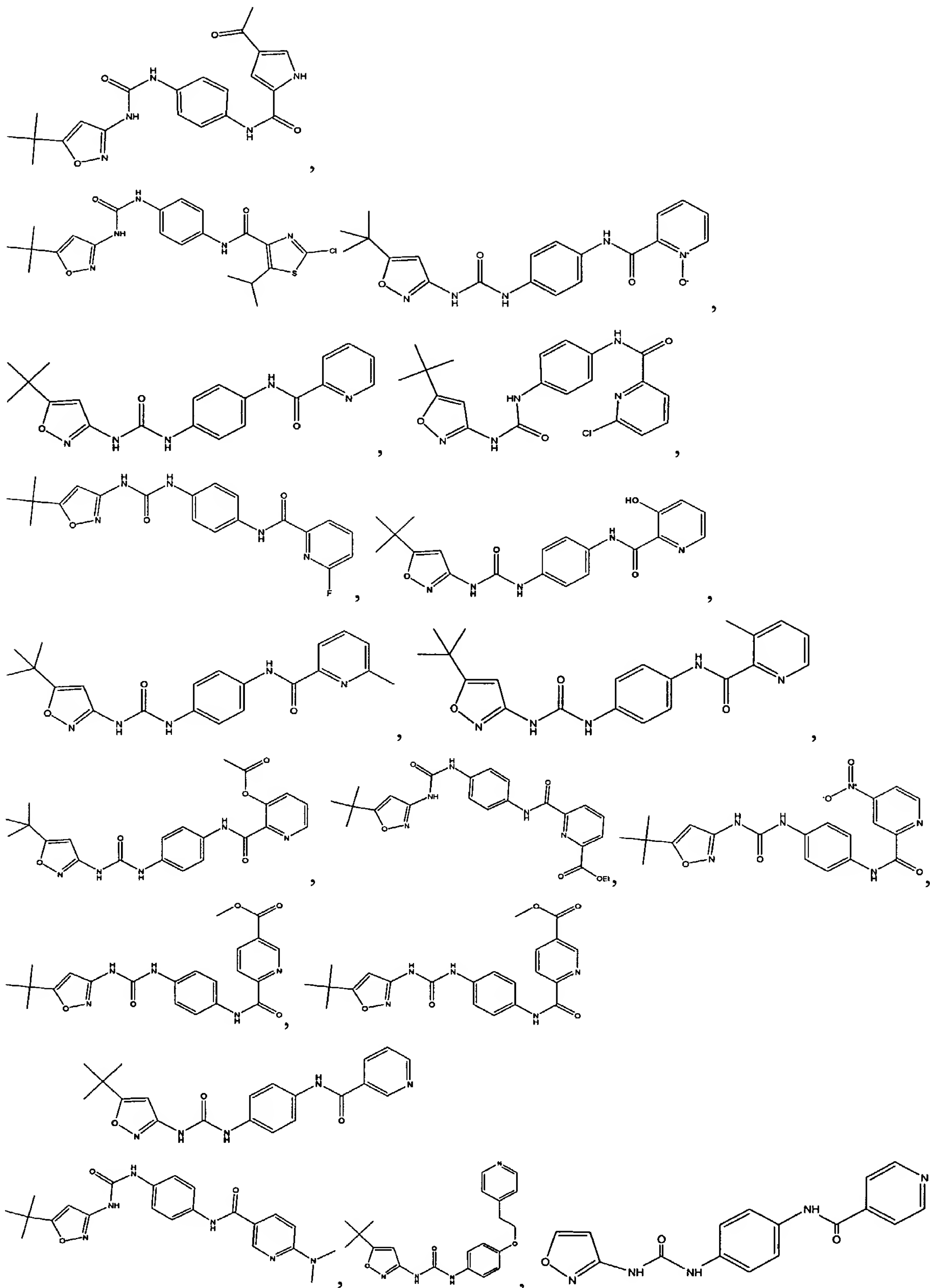
Provided herein are methods for modulating PDGF-R kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:

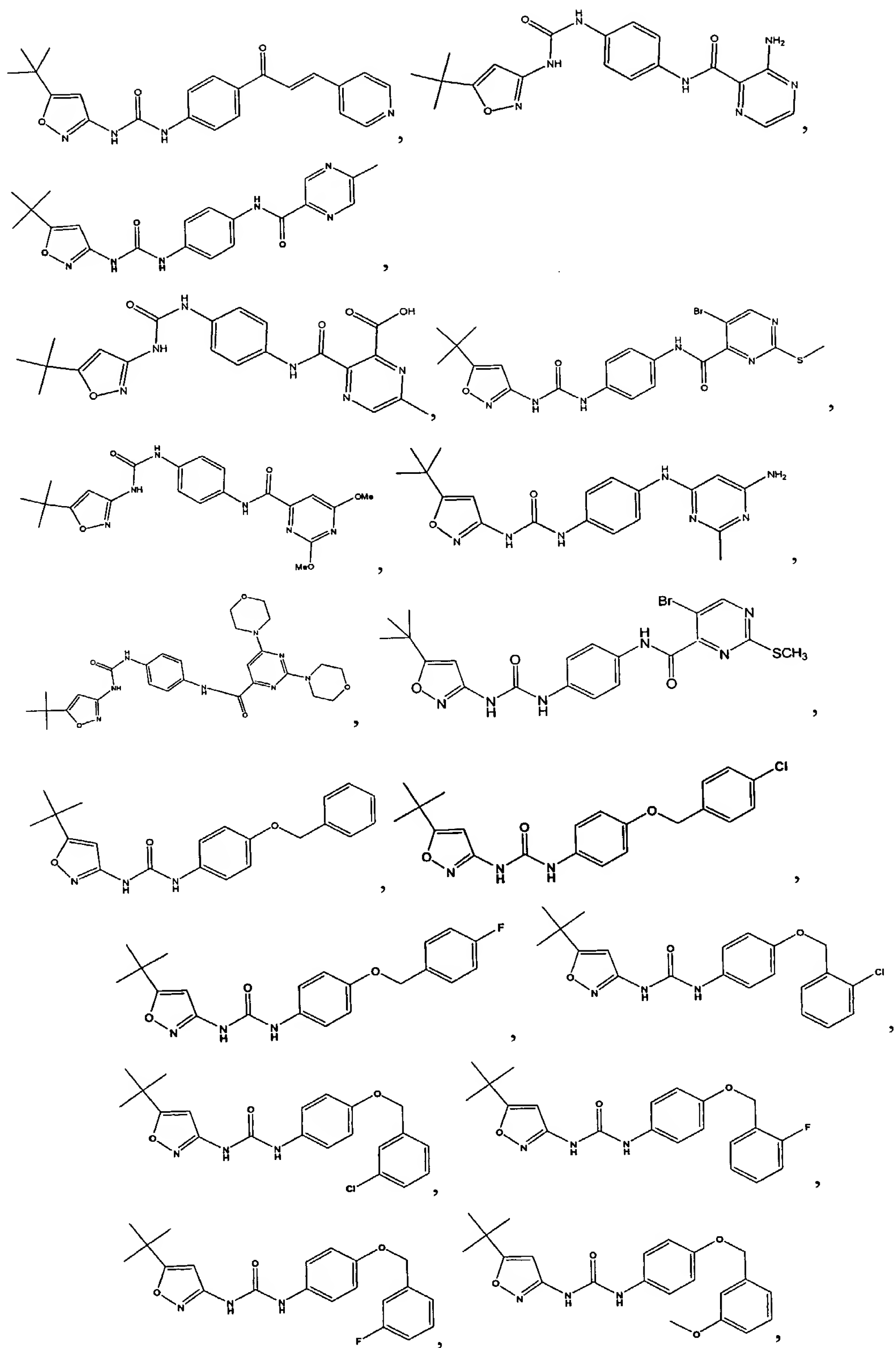


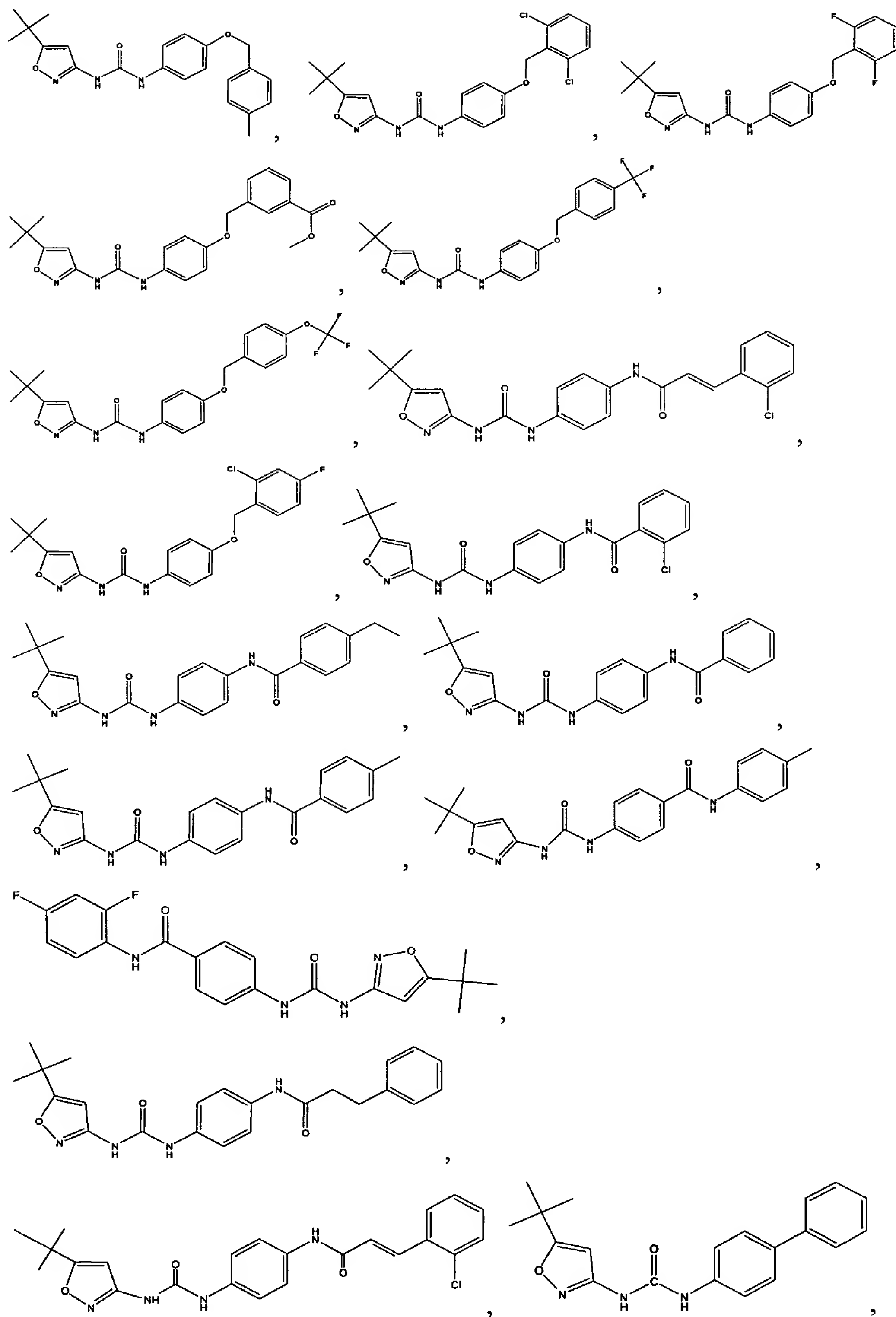


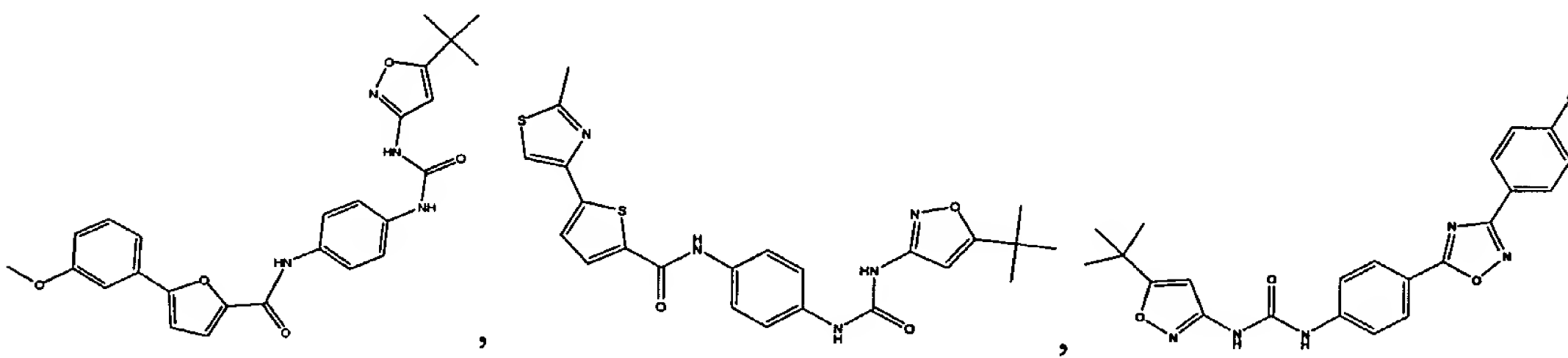
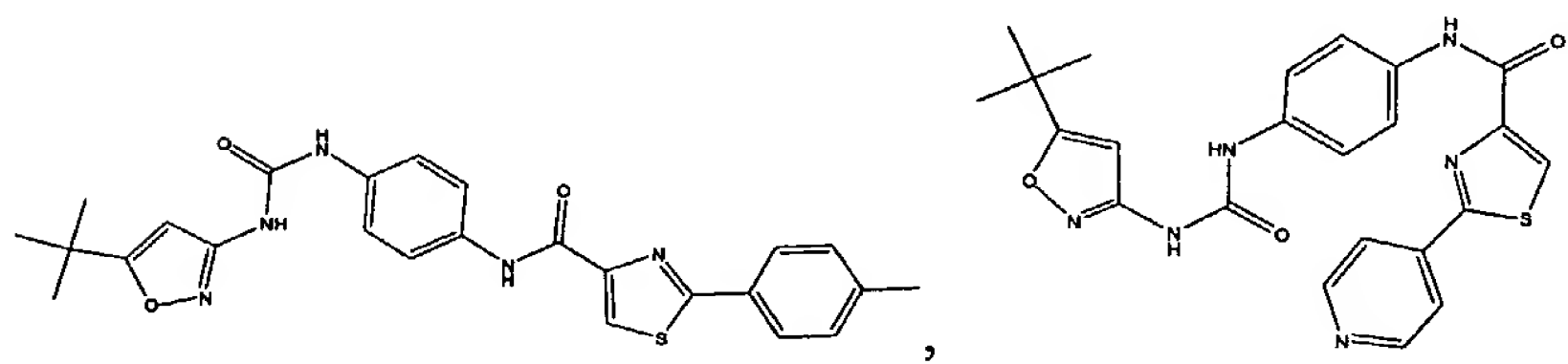
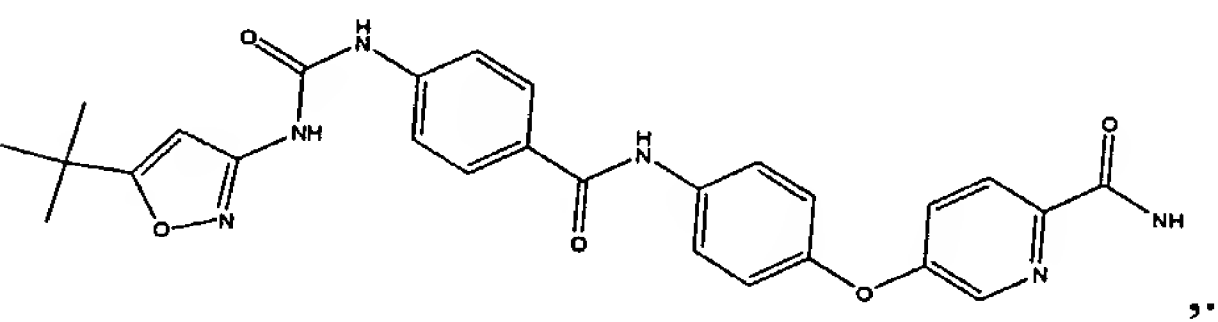
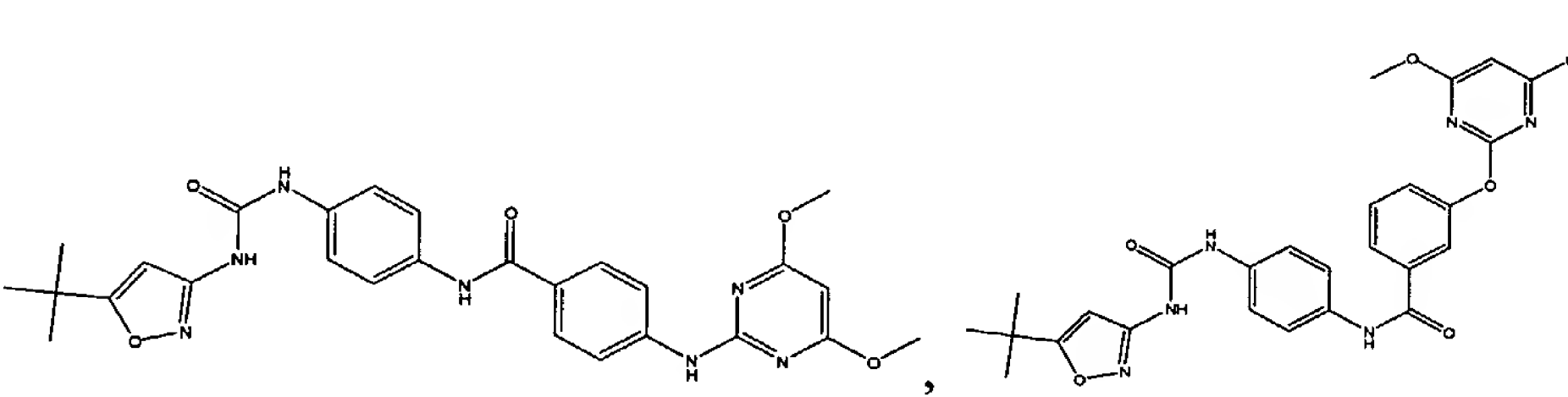
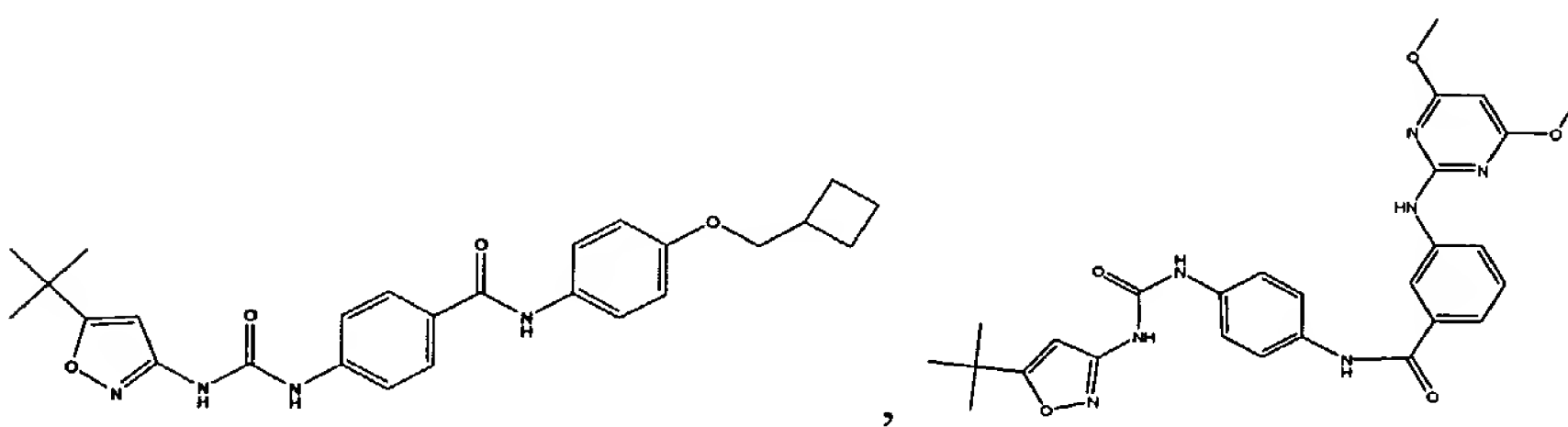
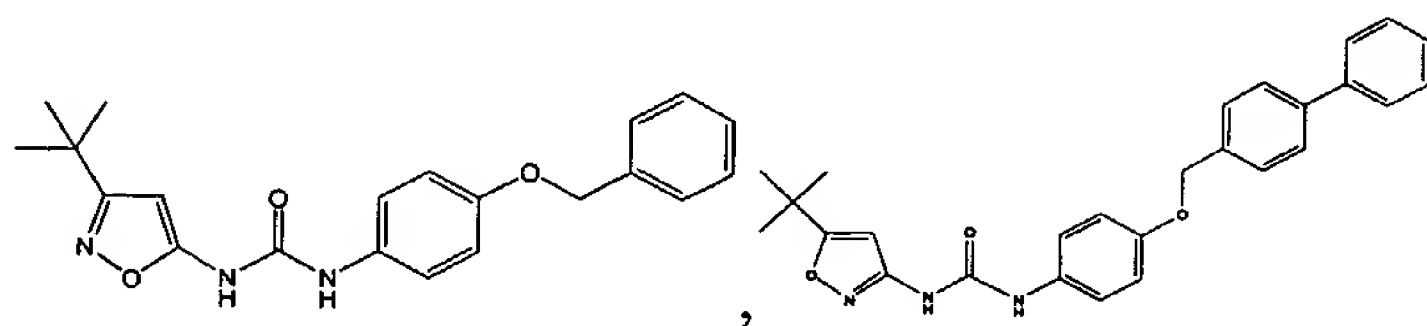
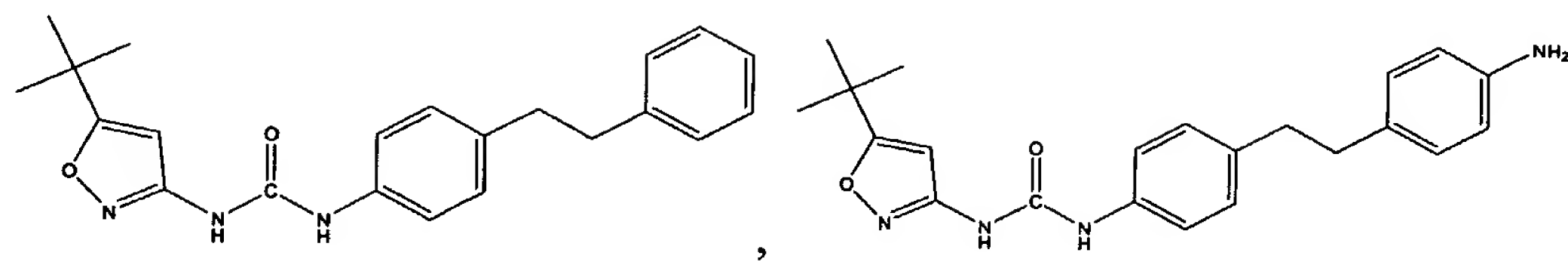


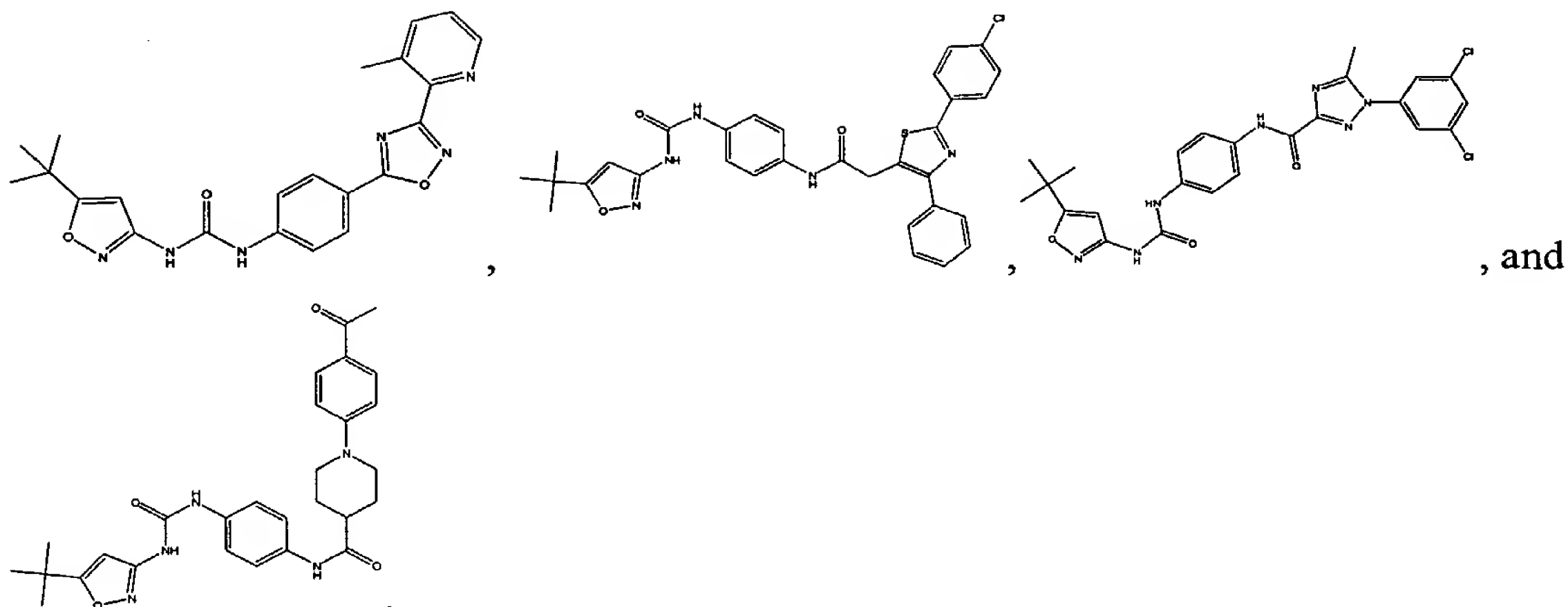






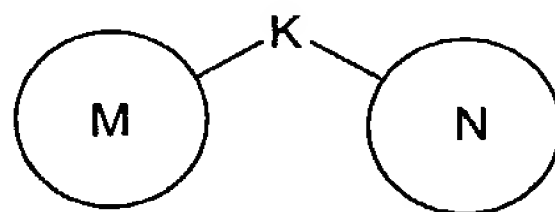






Exemplary C-KIT Modulators

5 Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:

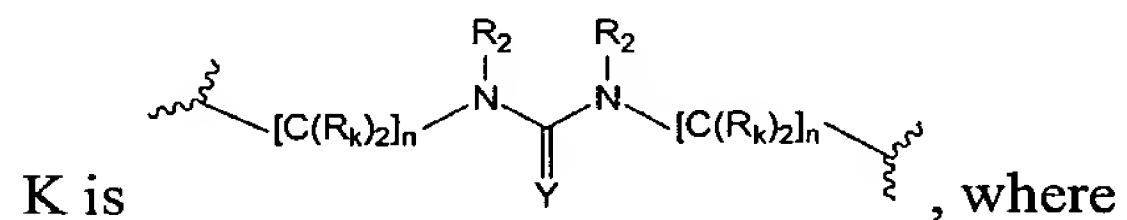


wherein:

M is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

10 N is a substituted or unsubstituted aryl, or substituted or unsubstituted hetroaryl;

and



Y is O or S;

each R_k is independently H, halogen, substituted or unsubstituted alkyl,

15 -OH, substituted or unsubstituted alkoxy, -OC(O) R_2 , -NO₂, -N(R_2)₂,

-SR₂, -C(O) R_2 , -C(O)₂ R_2 , -C(O)N(R_2)₂, or -N(R_2)C(O) R_2 ,

each R_2 is independently H, substituted or unsubstituted alkyl, substituted

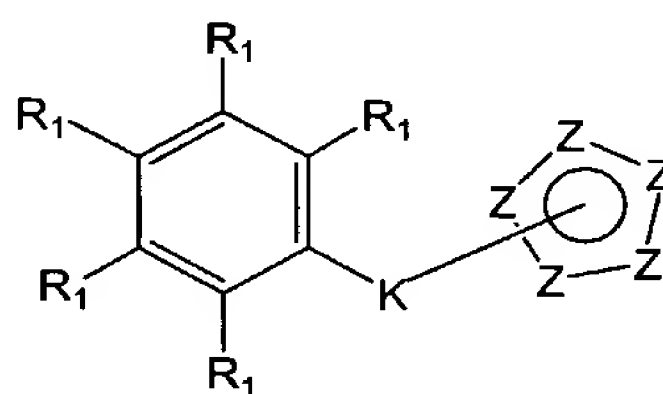
or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl,

substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

5 or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



10 wherein:

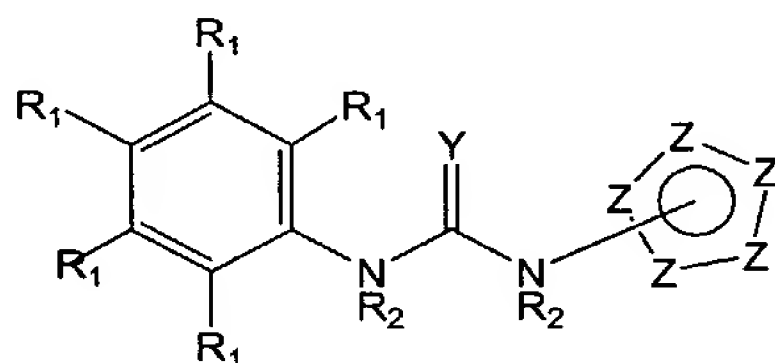
each Z is independently C, CR_3 , N, NR_3 , O, or S, provided that no more than two Z 's are heteroatoms and wherein no two adjacent Z 's are O or S,

15 where R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

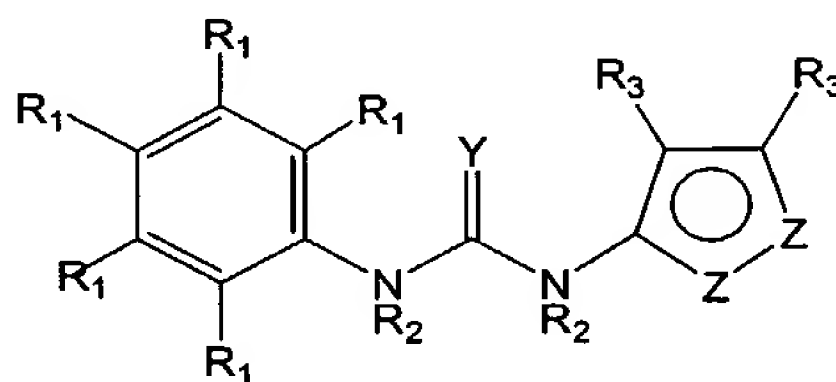
20 each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR_c$, $-OH$, $-OC(O)R_c$, $-NO_2$, $-N(R_c)_2$, $-SR_c$, $S(O)_jR_c$ where j is 1 or 2, $-NR_cC(O)R_c$, $-C(O)N(R_c)_2$, $-C(O)_2R_c$, or $-C(O)R_c$; or two adjacent R_1 's, are taken together to form a substituted or unsubstituted aryl or heteroaryl,

each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

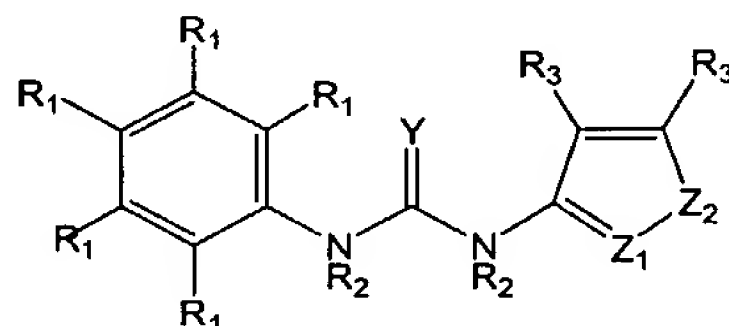
Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

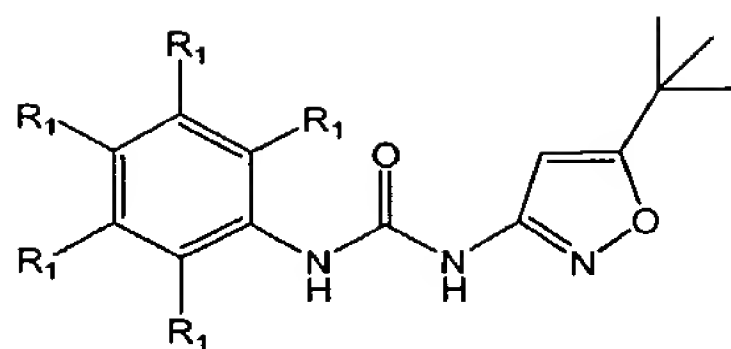


Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein Z_1 is CR_3 or N; and Z_2 is O or S.

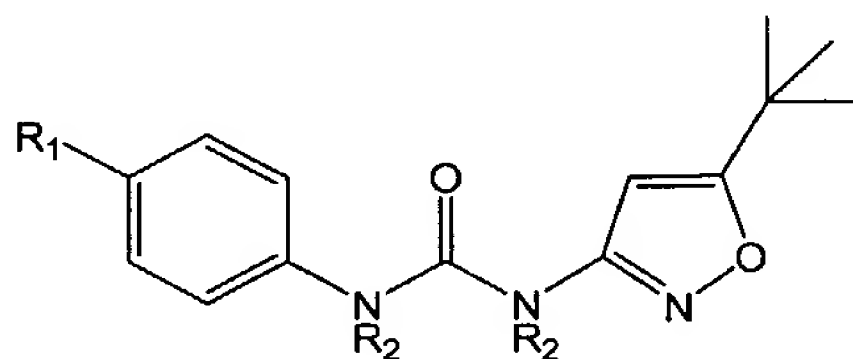
Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



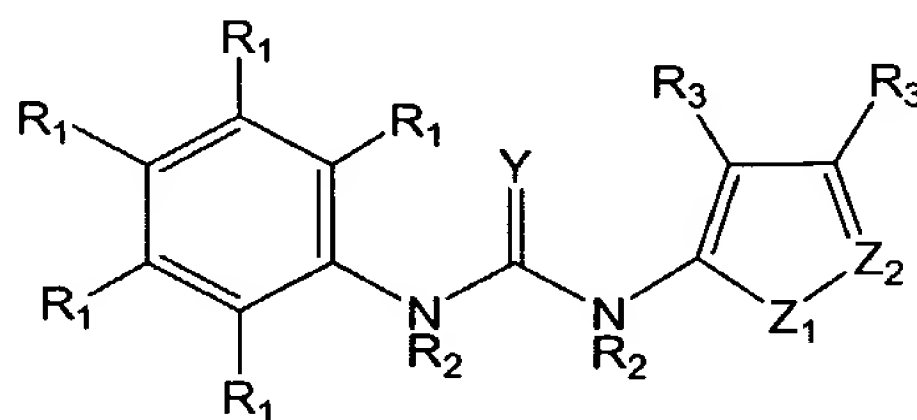
wherein:

each R_1 is independently H, halogen, substituted or unsubstituted alkyl,
 substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl,
 substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl,
 substituted or unsubstituted heteroaryl, $-OR_c$, $-OH$, $-OC(O)R_c$, $-NO_2$, $-N(R_c)_2$,
 $-SR_c$, $S(O)_jR_c$ where j is 1 or 2, $-NR_cC(O)R_c$, $-C(O)N(R_c)_2$, $-C(O)_2R_c$, or
 $-C(O)R_c$; or two adjacent R_1 's, are taken together to form a substituted or
 unsubstituted aryl or heteroaryl.

Methods for modulating c-kit kinase, said method comprising administering an effective
 amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the
 following structure are provided herein:



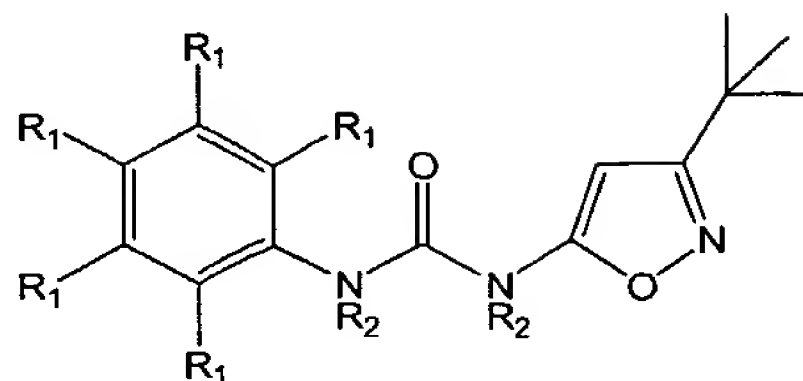
Methods for modulating c-kit kinase, said method comprising administering an effective
 amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the
 following structure are provided herein:



wherein Z_1 is O or S; and Z_2 is CR_3 or N.

Methods for modulating c-kit kinase, said method comprising administering an effective
 amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the

following structure are provided herein:

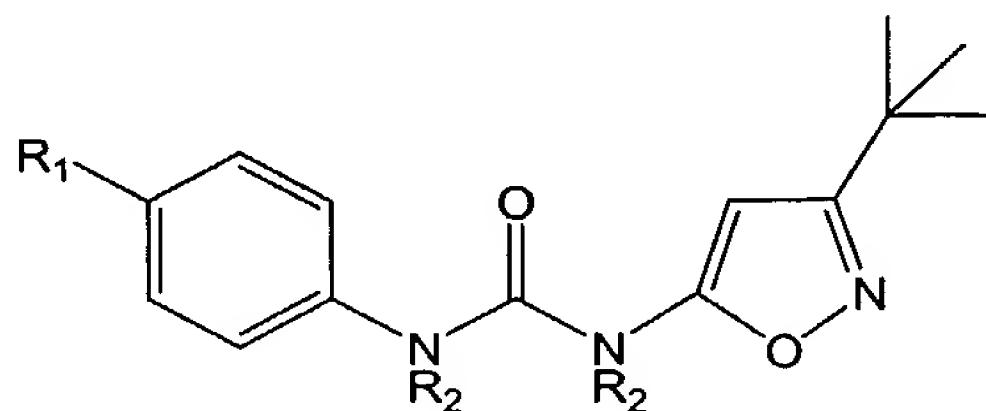


wherein:

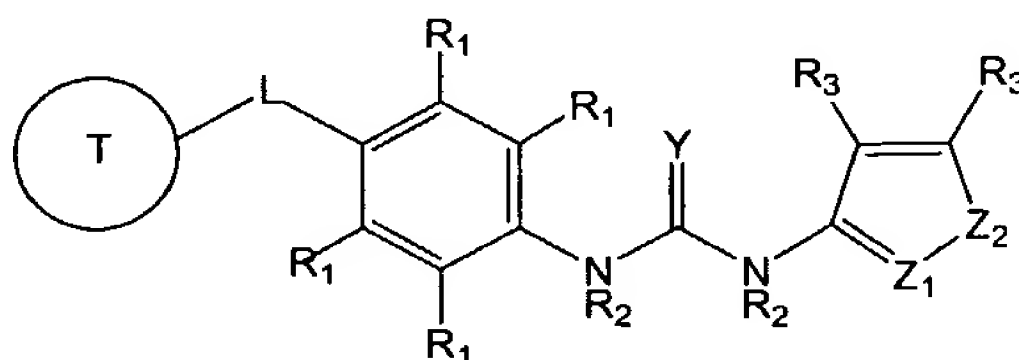
each R_1 is independently H, halogen, substituted or unsubstituted alkyl,
 -O(substituted or unsubstituted alkyl), -O(substituted or unsubstituted
 alkenyl), -NR_cC(O)O(substituted or unsubstituted alkyl), -NR_cC(O)
 (substituted or unsubstituted alkyl), -NR_cC(O)(substituted or unsubstituted
 alkenyl), -C(O)NR_c(substituted or unsubstituted alkyl),
 -C(O)NR_c(substituted or unsubstituted alkenyl), -NO₂, -S(=O)R_c, -SR_c,
 -C(O)₂R_c, or -C(O)R_c; and

each R_2 is independently H or substituted or unsubstituted alkyl.

Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



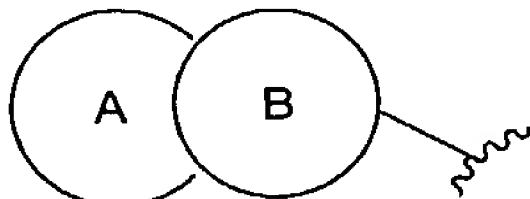
Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



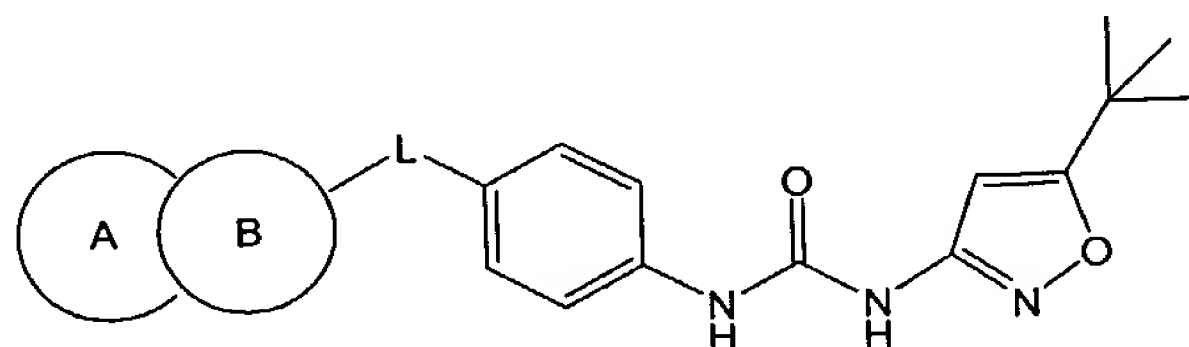
wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-C(O)NH-$, $-C(O)-$, $-NH-$, $-O-$, $-S-$, $-O(\text{substituted or unsubstituted alkylene})-$, $-N(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkenylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkenylene})-$, $-C(O)(\text{substituted or unsubstituted alkenylene})-$, and $-NHC(O)(\text{substituted or unsubstituted alkylene})S(\text{substituted or unsubstituted alkylene})C(O)NH-$; and

T is a mono-, bi-, or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

In some embodiments, T is  wherein A is a substituted or unsubstituted five or six-membered heterocyclyl, aryl, or heteroaryl; and B is a substituted or unsubstituted five or six-membered heterocyclene, arylene, or heteroarylene, wherein A and B together form a fused two ring moiety.

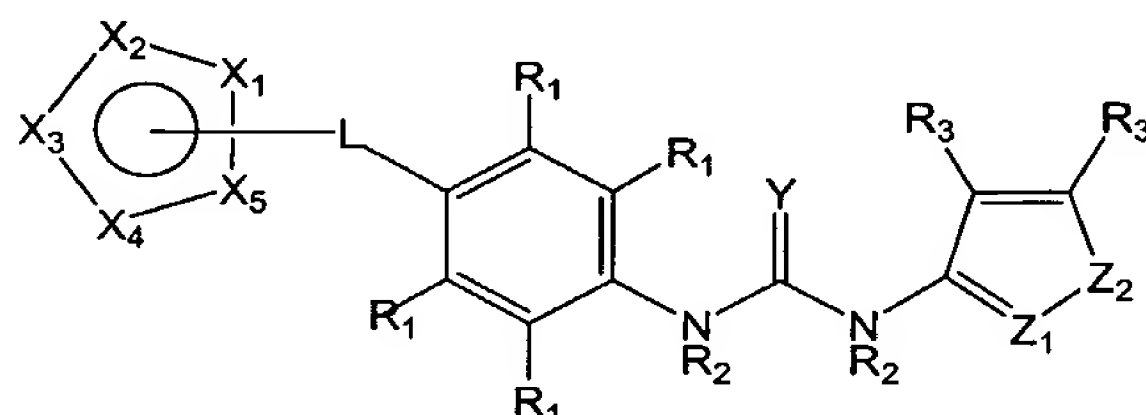
Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



In some embodiments, L of said compound is a covalent bond, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-O(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH-$, or $-NHC(O)(\text{alkylene})-$. In other embodiments, B of said compound is a substituted or unsubstituted five-membered heteroarylene. In still other embodiments, B of said compound is a substituted or unsubstituted 6-membered arylene or heteroarylene. In some

embodiments, T of said compound is a tricyclic, substituted or unsubstituted aryl, heterocyclyl, or heteroaryl.

Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein:

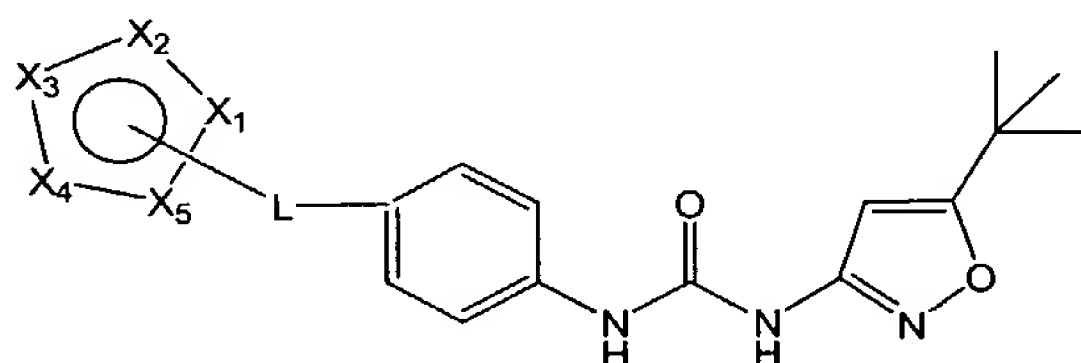
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, -C(O)NH-, -C(O)-, -NH-, -O-, -S-, -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -C(O)(substituted or unsubstituted alkenylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

each of X₁-X₅ is independently C, CR, N, NR, S, or O, wherein no more than three of X₁-X₅ is a heteroatom, and no two adjacent ring atoms are O or S; where

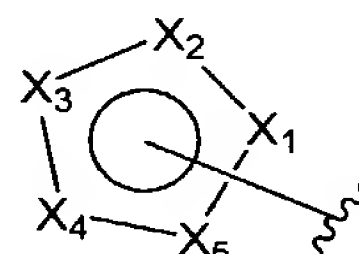
each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O)R_d, -NO₂, -N(R_d)₂, -SR_d, -S(O)_jR_d where j is 1 or 2, -NR_d C(O)R_d, -C(O)₂R_d, -C(O)N(R_d)₂ or -C(O)R_d, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

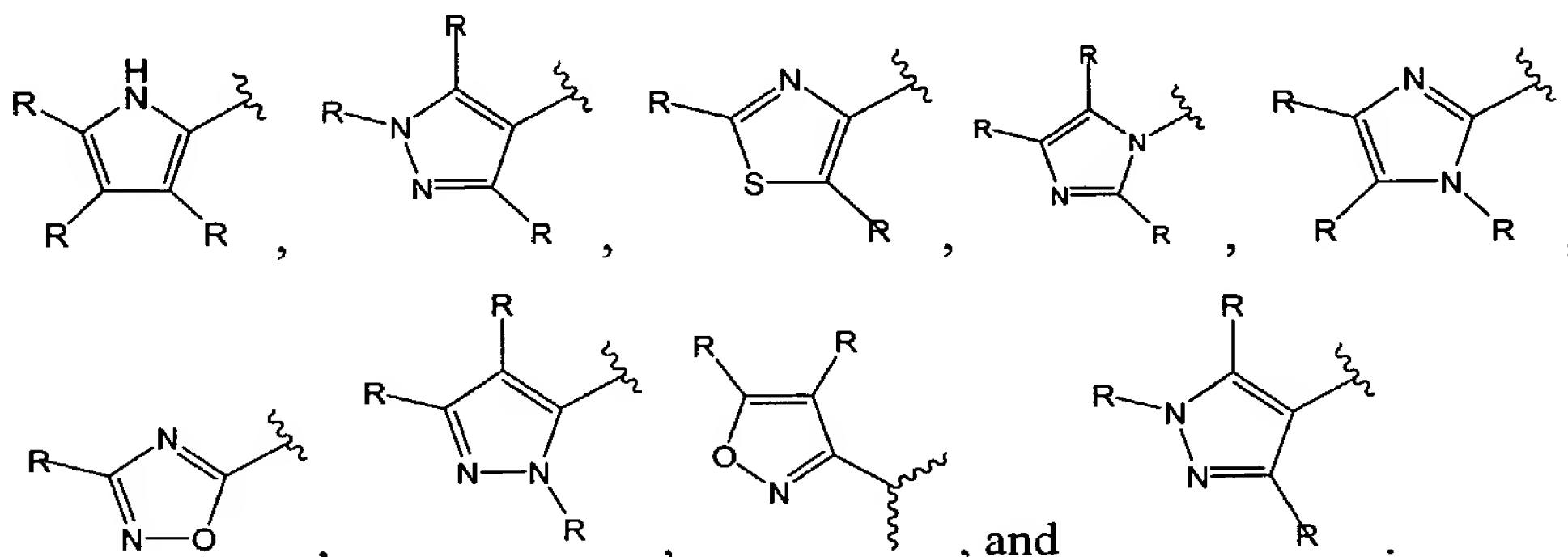
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

5 Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

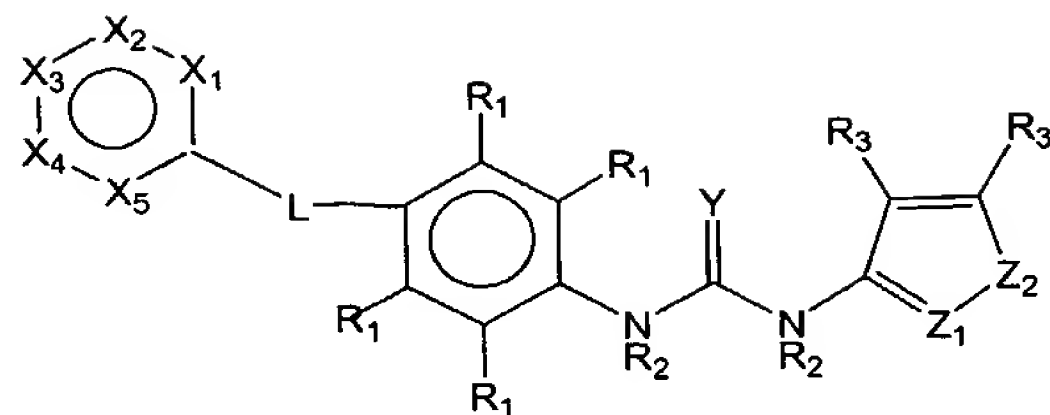


In some embodiments, L of said compound is a covalent bond, -C(O)NH-, or -O(substituted

10 or unsubstituted alkylene)-. In other embodiments,  of said compound is selected from the group consisting of: .



15 Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



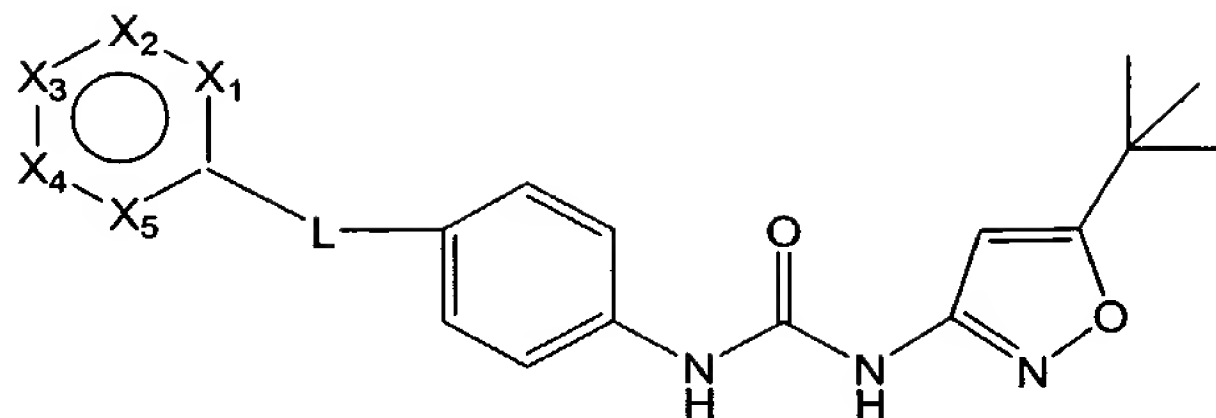
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{O}(\text{substituted or unsubstituted alkylene})-$, $-\text{N}(\text{substituted or unsubstituted alkylene})-$, $-\text{C}(\text{O})\text{NH}(\text{substituted or unsubstituted alkylene})-$, $\text{C}(\text{O})\text{NH}(\text{substituted or unsubstituted alkenylene})-$, $-\text{NHC}(\text{O})(\text{substituted or unsubstituted alkylene})-$, $-\text{NHC}(\text{O})(\text{substituted or unsubstituted alkenylene})-$, $-\text{C}(\text{O})(\text{substituted or unsubstituted alkenylene})-$, and $-\text{NHC}(\text{O})(\text{substituted or unsubstituted alkylene})\text{S}(\text{substituted or unsubstituted alkylene})\text{C}(\text{O})\text{NH}-$; and

each of X_1 - X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1 - X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where

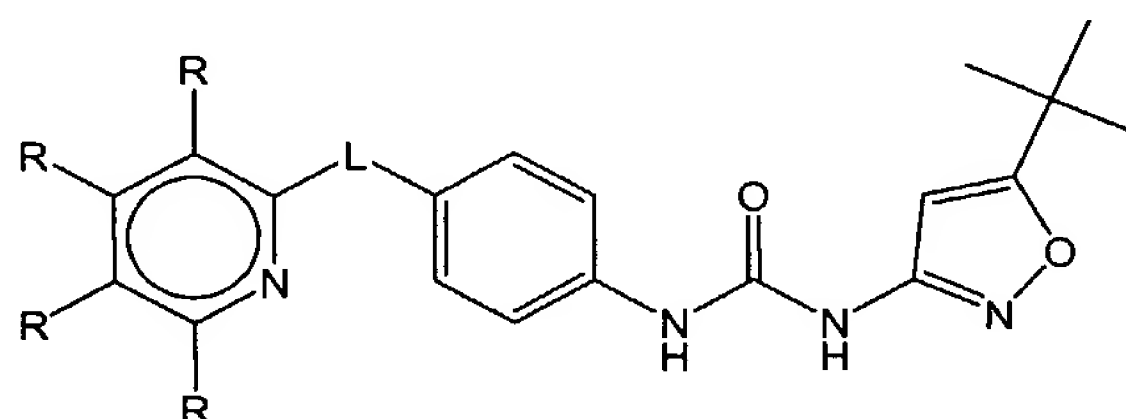
each R is independently H, halogen, substituted or unsubstituted alkyl, $-\text{OH}$, substituted or unsubstituted alkoxy, $-\text{OC}(\text{O})\text{R}_d$, $-\text{NO}_2$, $-\text{N}(\text{R}_d)_2$, $-\text{SR}_d$, $-\text{S}(\text{O})_j\text{R}_d$ where j is 1 or 2, $-\text{NR}_d$, $\text{C}(\text{O})\text{R}_d$, $-\text{C}(\text{O})_2\text{R}_d$, $-\text{C}(\text{O})\text{N}(\text{R}_d)_2$ or $-\text{C}(\text{O})\text{R}_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

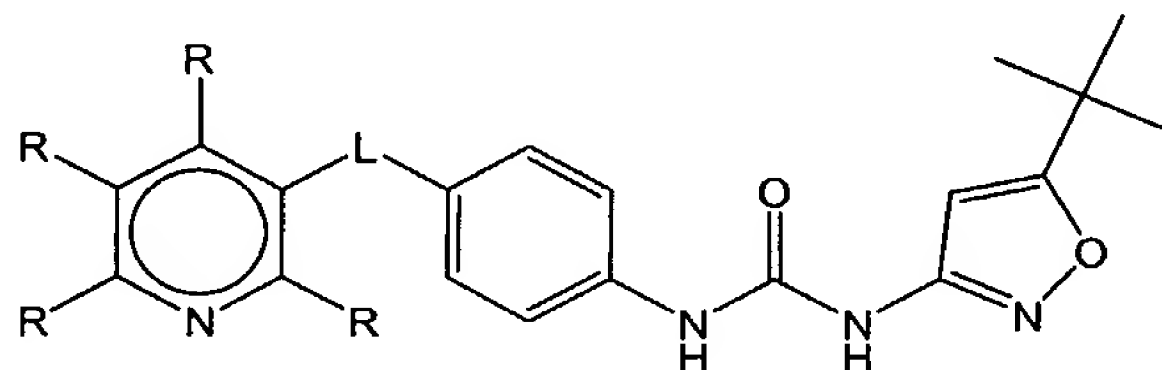


Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

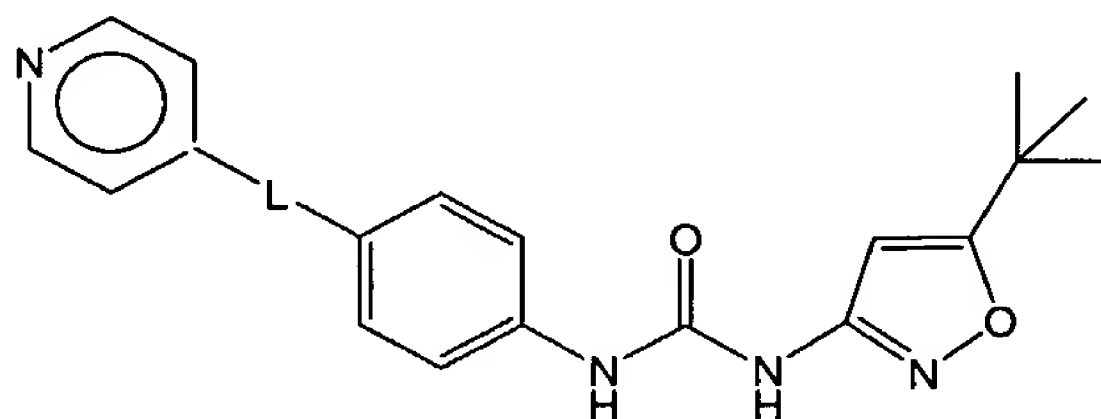


5

Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

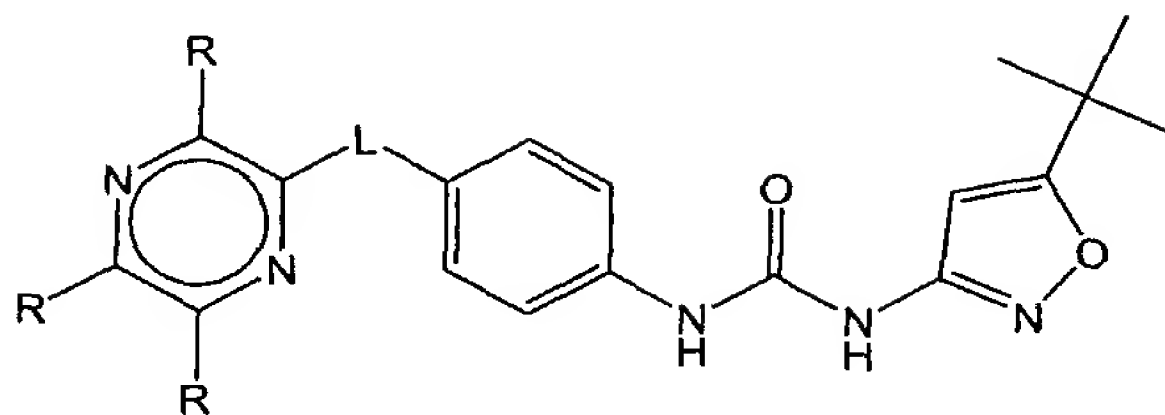


10 Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

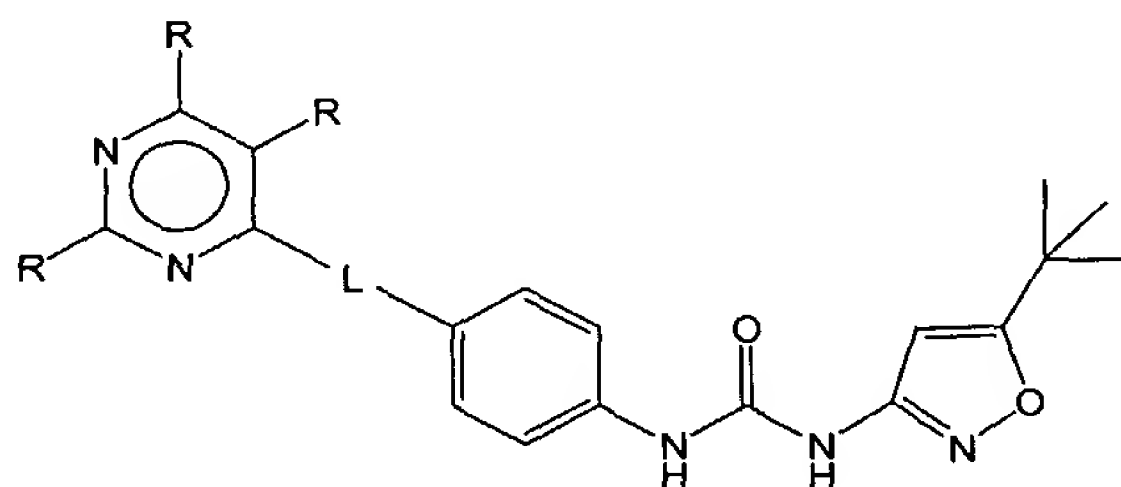


15 Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the

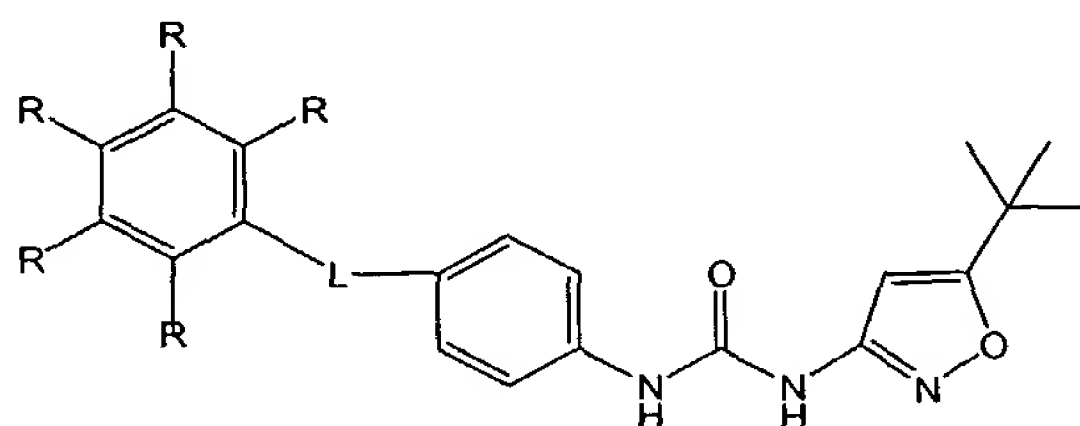
following structure are provided herein:



Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



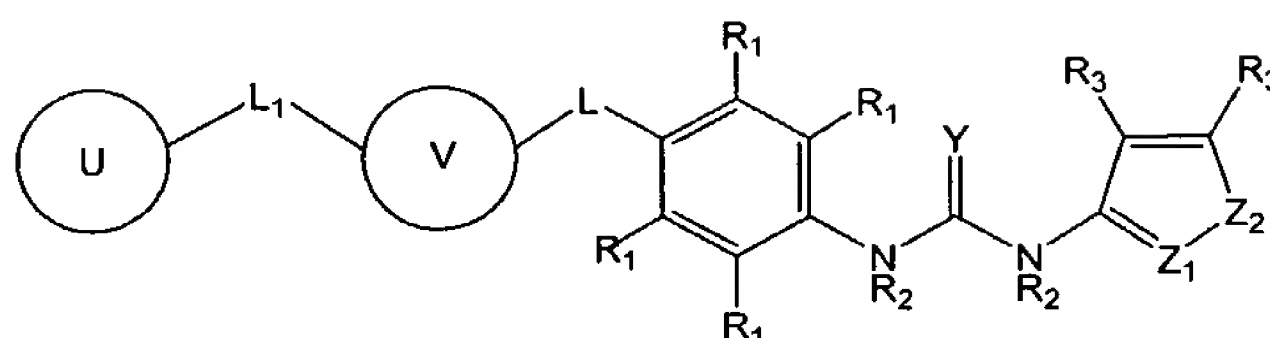
Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



In some embodiments, L of said compound is -NHC(O)-, -NHC(O)(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene), or -NHC(O)(substituted or unsubstituted alkenylene)-. In other embodiments, L of said compound is -O- or -O(substituted or unsubstituted alkylene)-. In yet other embodiments, L of said compound is -(substituted or unsubstituted alkylene)- or -NHC(O)(alkylene)S(alkylene)C(O)NH-.

Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the

following structure are provided herein:



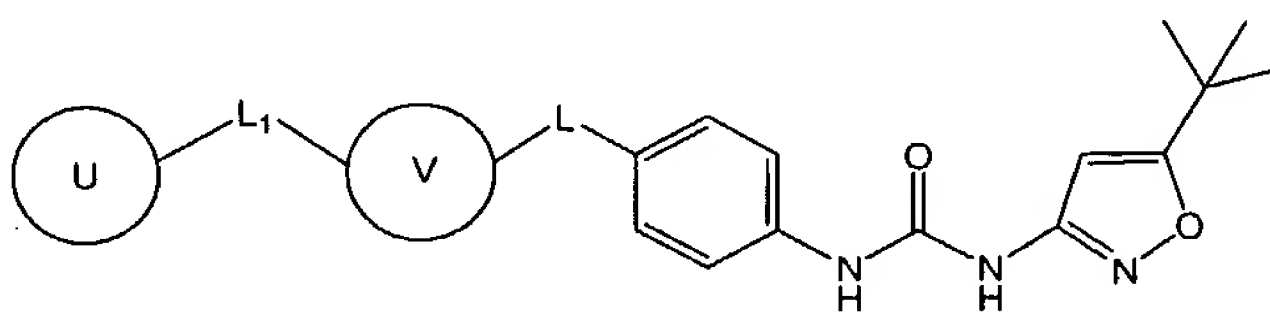
wherein:

L_1 is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, $-C(O)NH-$, $-C(O)-$, $-NH-$, $-O-$, $-S-$, $-O(\text{substituted or unsubstituted alkylene})-$, $-N(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, $-C(O)NH(\text{substituted or unsubstituted alkenylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkylene})-$, $-NHC(O)(\text{substituted or unsubstituted alkenylene})-$, $-C(O)(\text{substituted or unsubstituted alkenylene})-$, and $-NHC(O)(\text{substituted or unsubstituted alkylene})S(\text{substituted or unsubstituted alkylene})C(O)NH-$; and

U is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

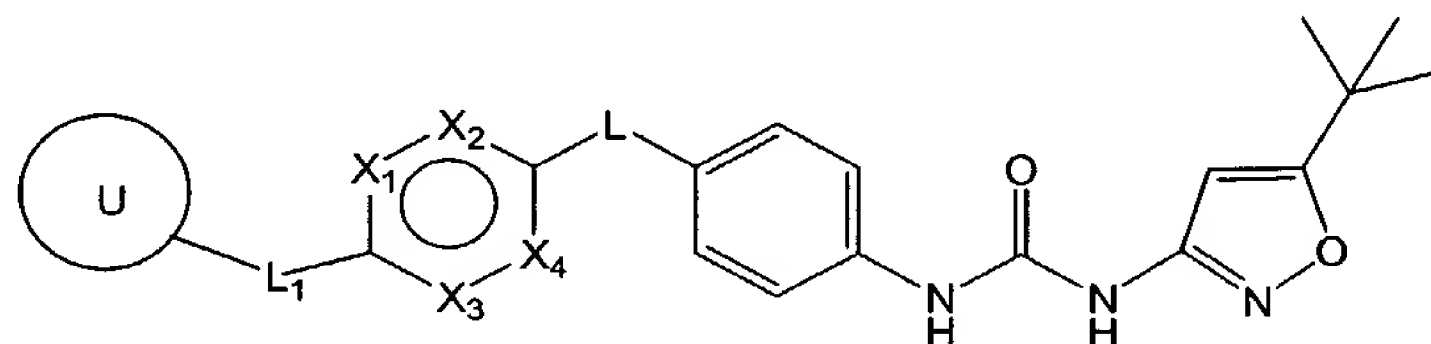
Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



In some embodiments, L_1 of said compound is a bond, $-O(\text{substituted or unsubstituted alkylene})-$, $-(\text{substituted or unsubstituted alkylene})-$, or $-S-$; and L of said compound is a covalent bond, $-C(O)NH-$, $-C(O)NH(\text{substituted or unsubstituted alkylene})-$, or -

NHC(O)(substituted or unsubstituted alkylene)-. In other embodiments, V of said compound is substituted or unsubstituted 5-membered heteroarylene.

Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:



wherein:

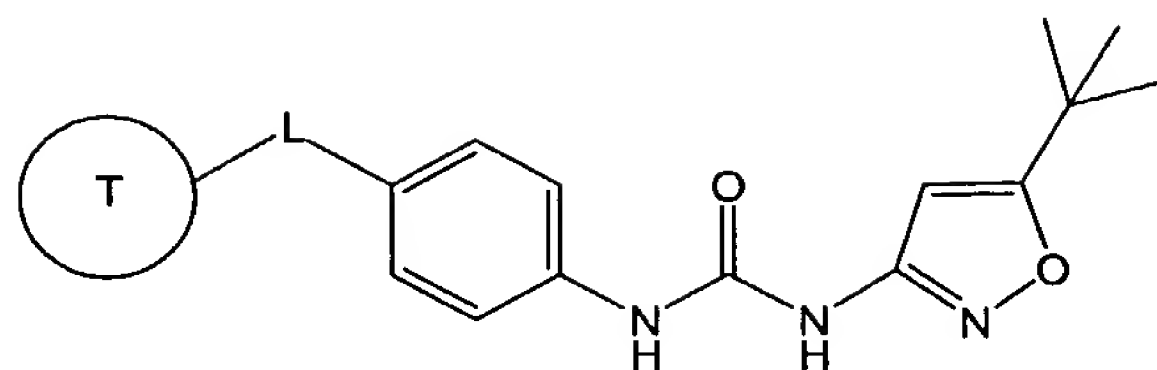
each of X_1 - X_4 is independently C, CR, or N, wherein no more than two of X_1 - X_5 is N;
where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-S(O)_jR_d$ where j is 1 or 2, $-NR_d C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$ or $-C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

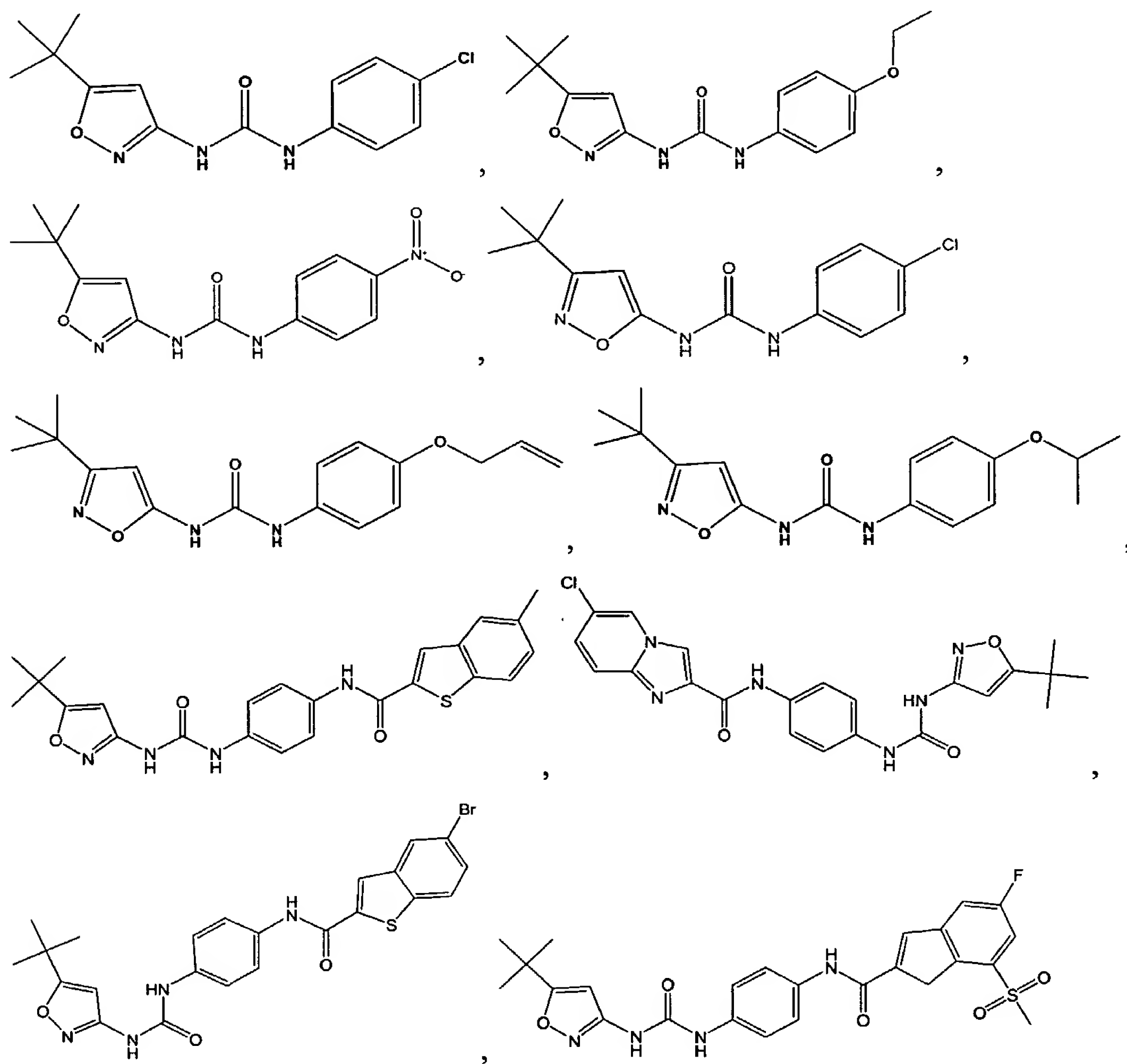
In some embodiment, U of said compound is substituted or unsubstituted pyrimidinyl or pyridinyl. In other embodiments, U of said compound is substituted or unsubstituted phenyl.

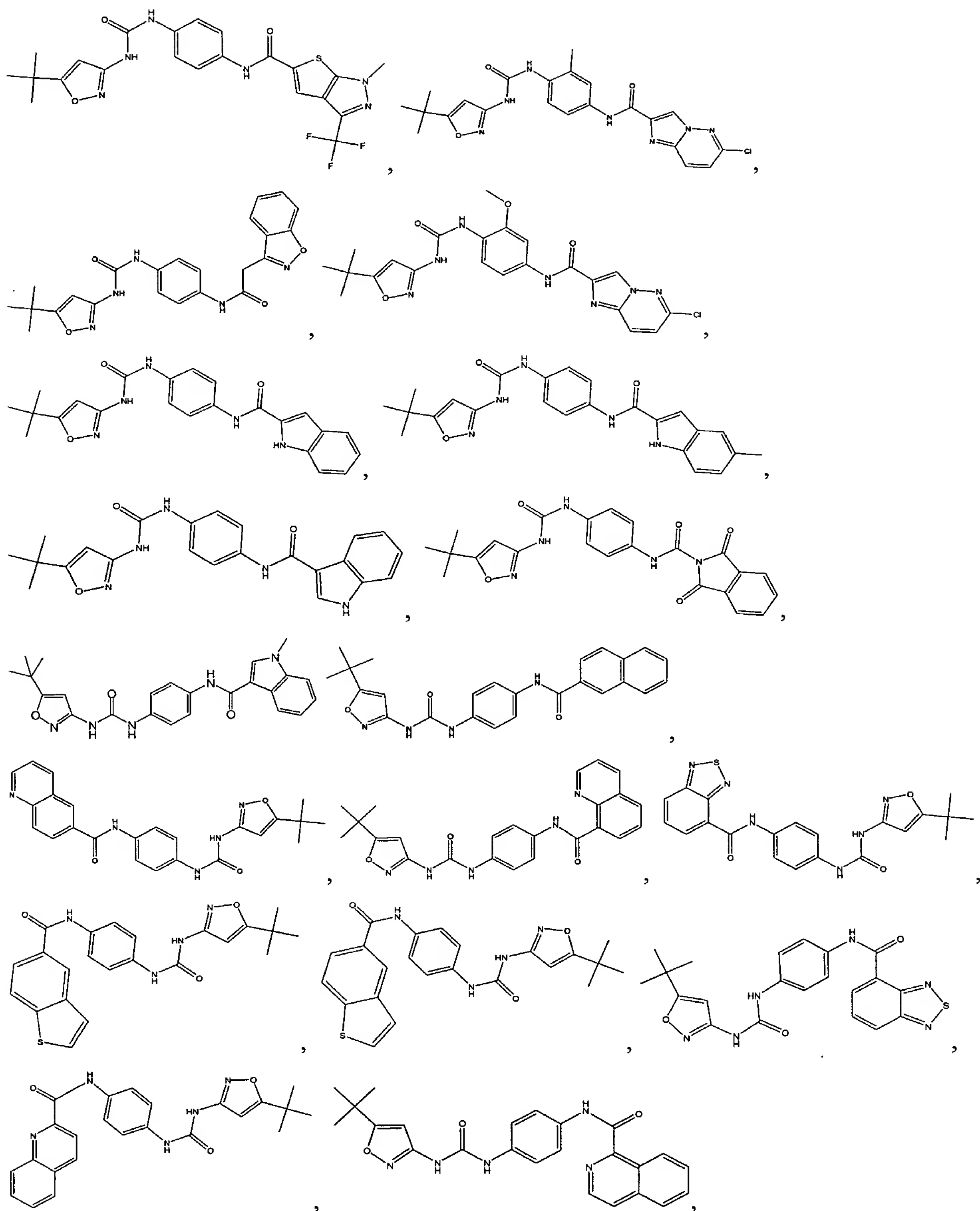
Methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to the following structure are provided herein:

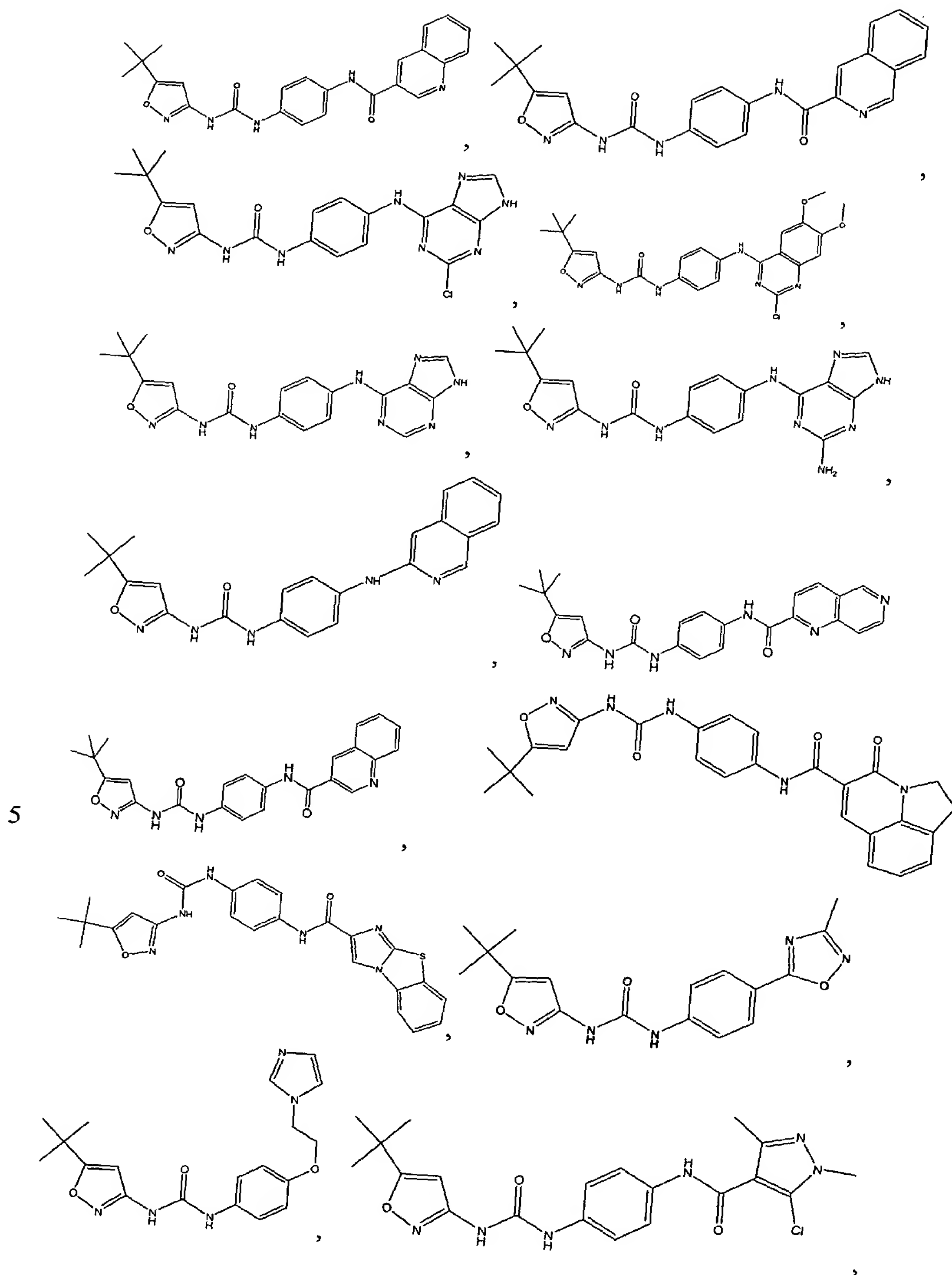


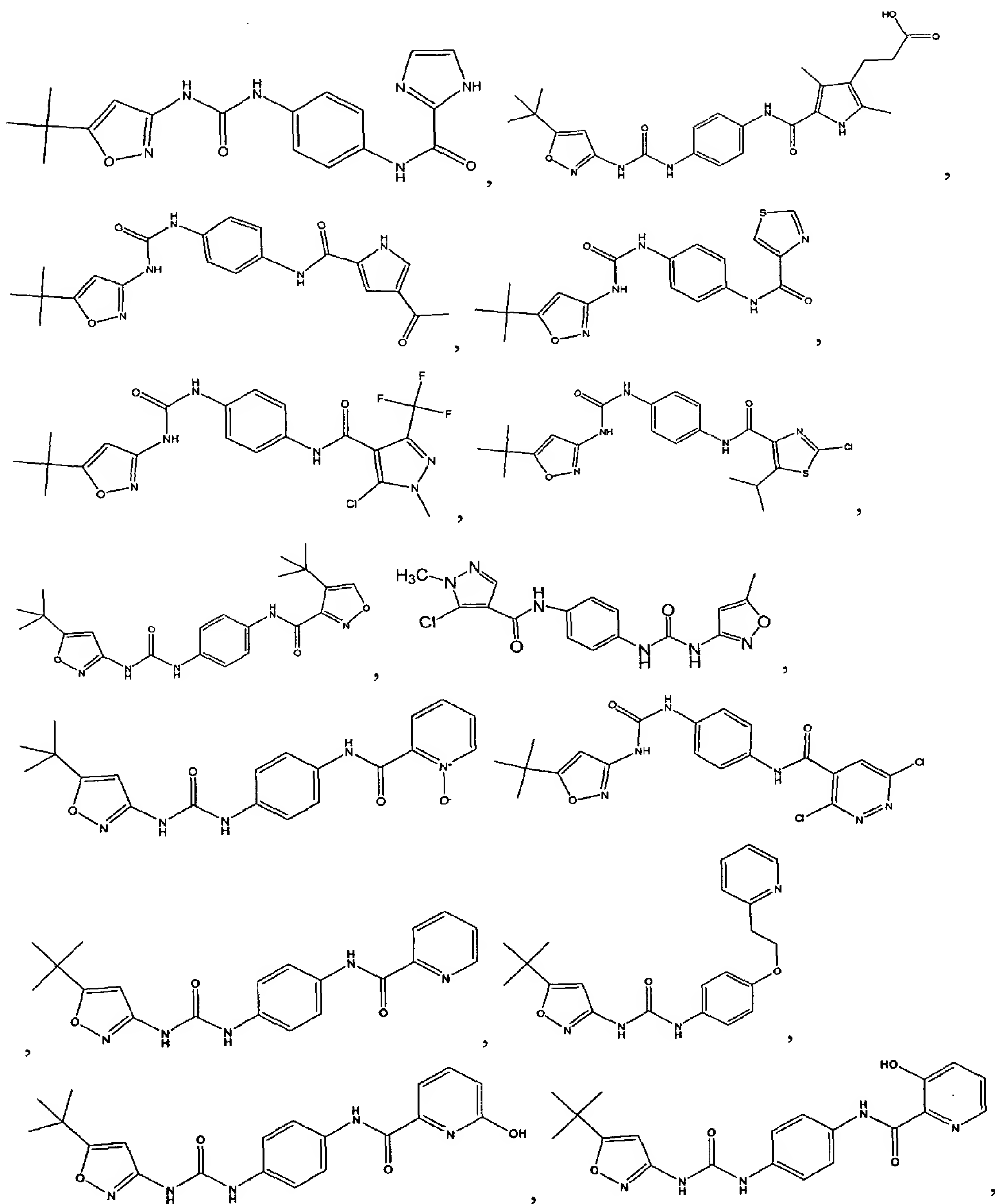
wherein T is substituted or unsubstituted cycloalkyl or heterocyl.

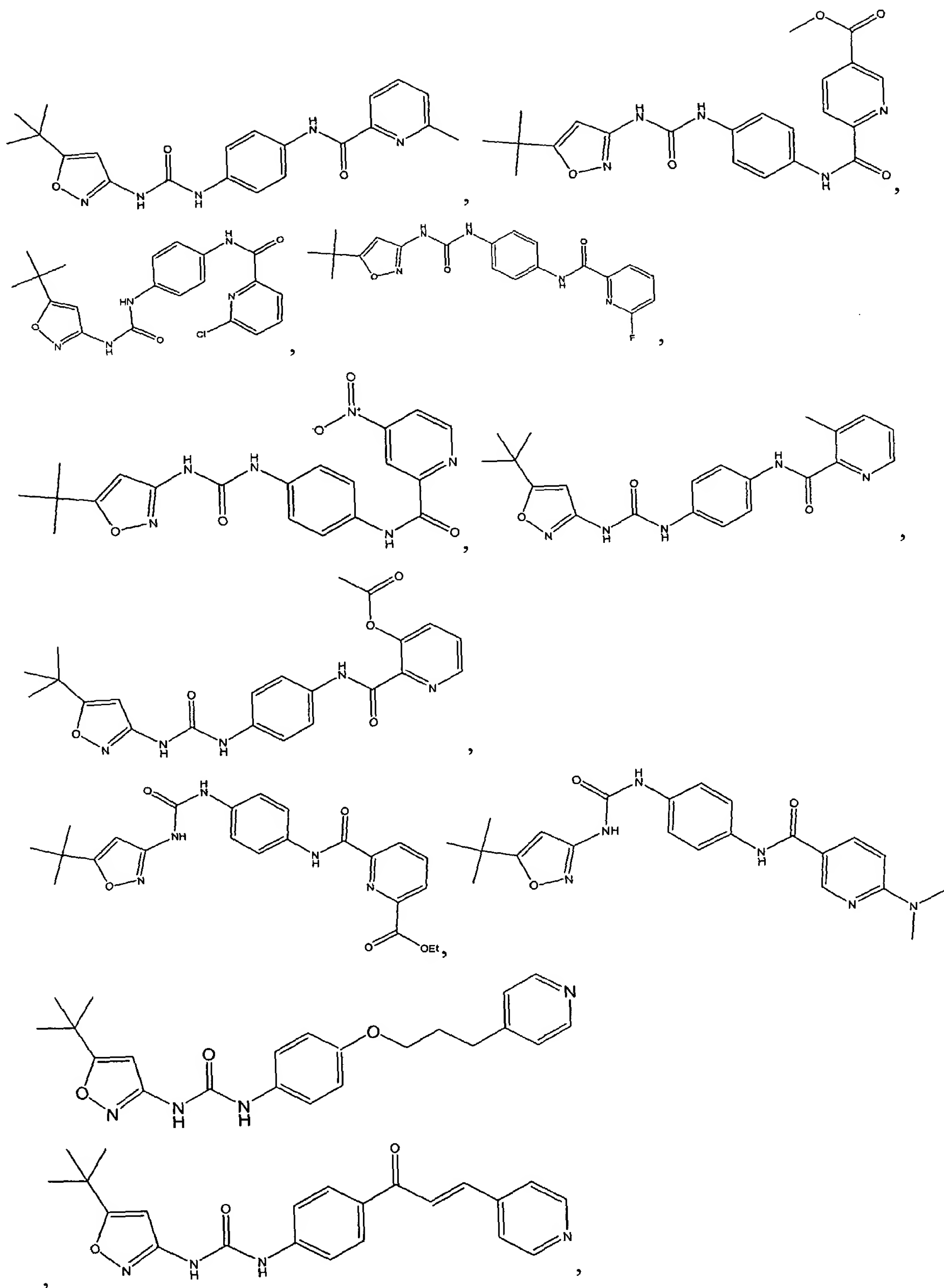
Provided herein are methods for modulating c-kit kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:

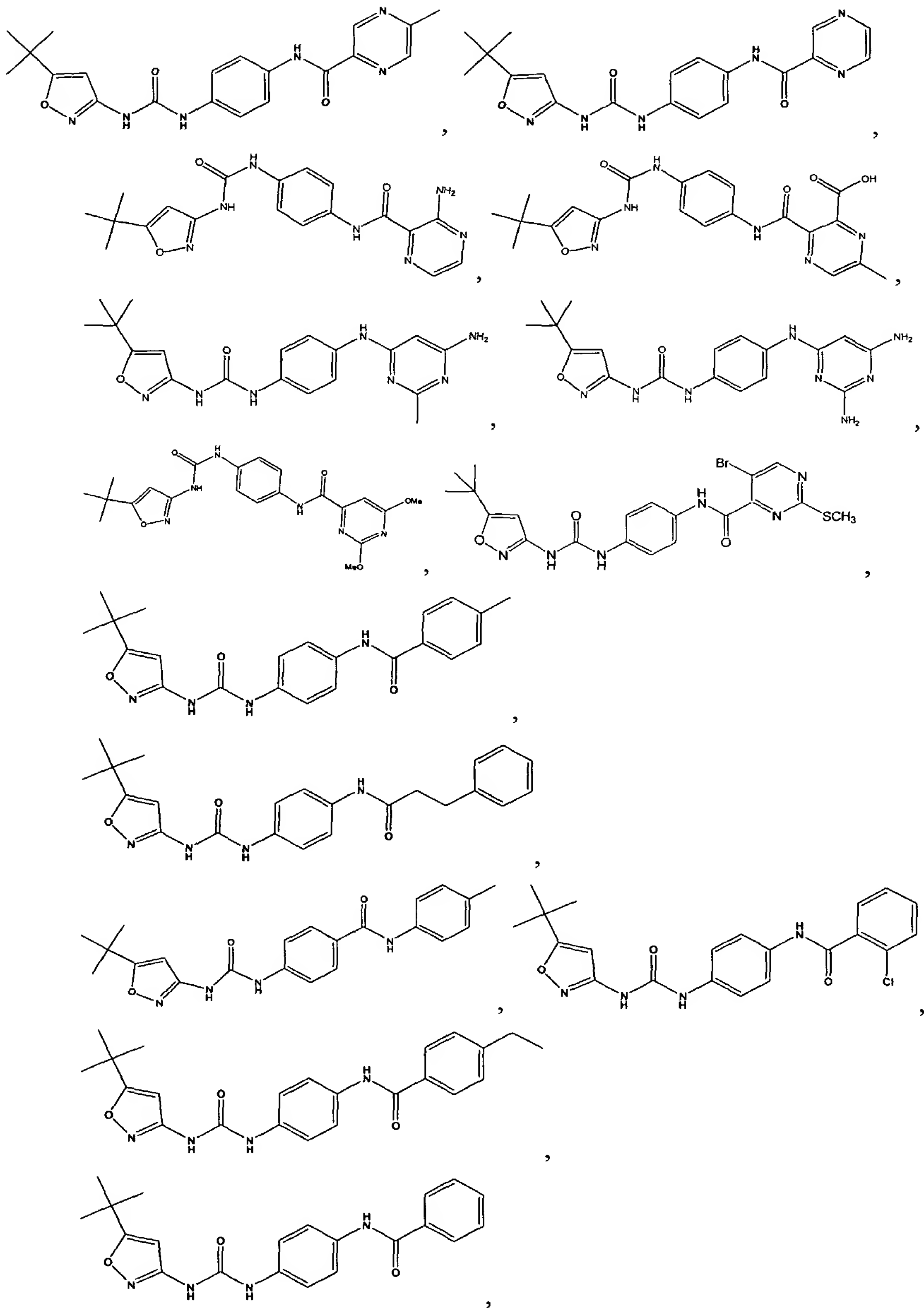


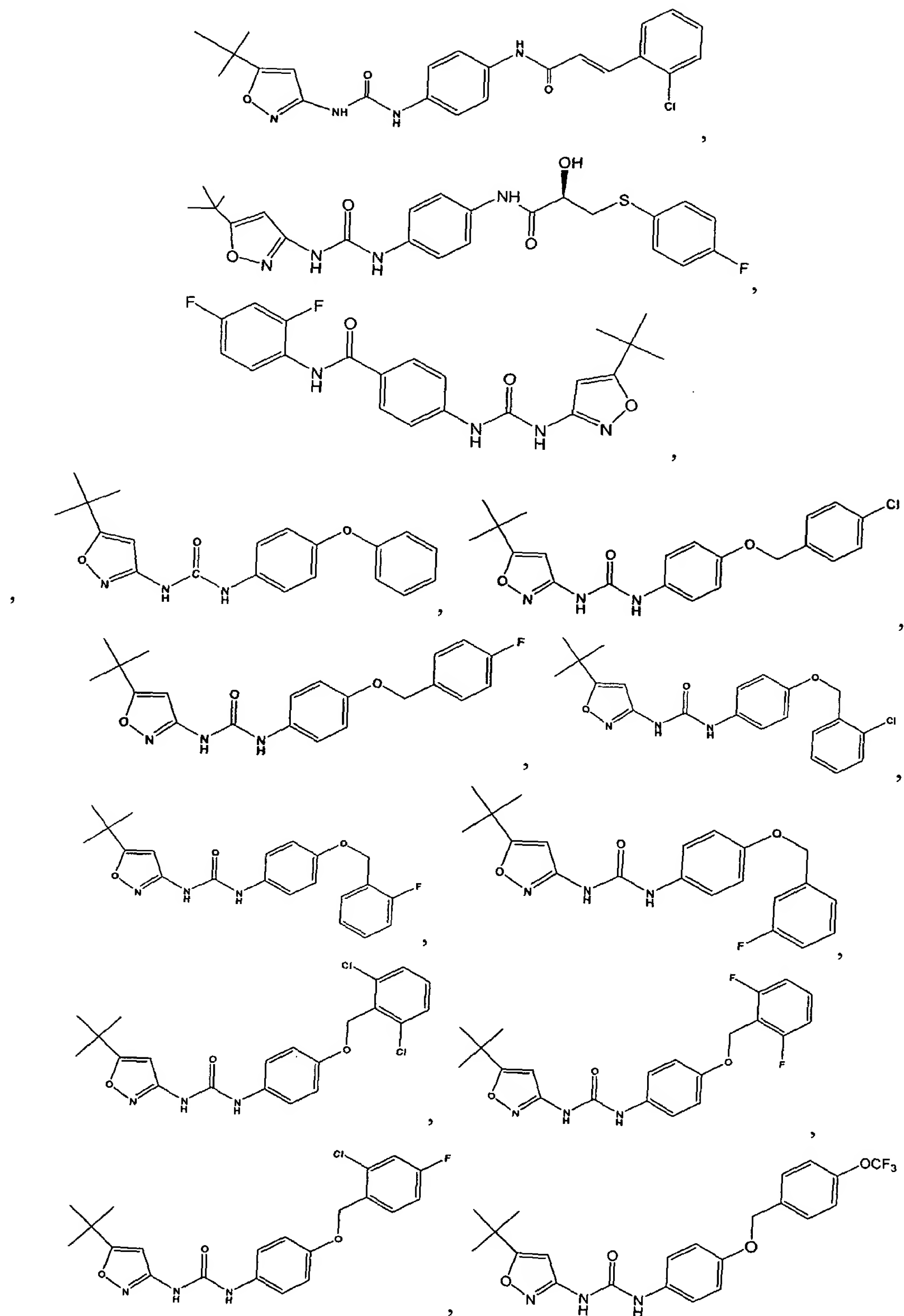


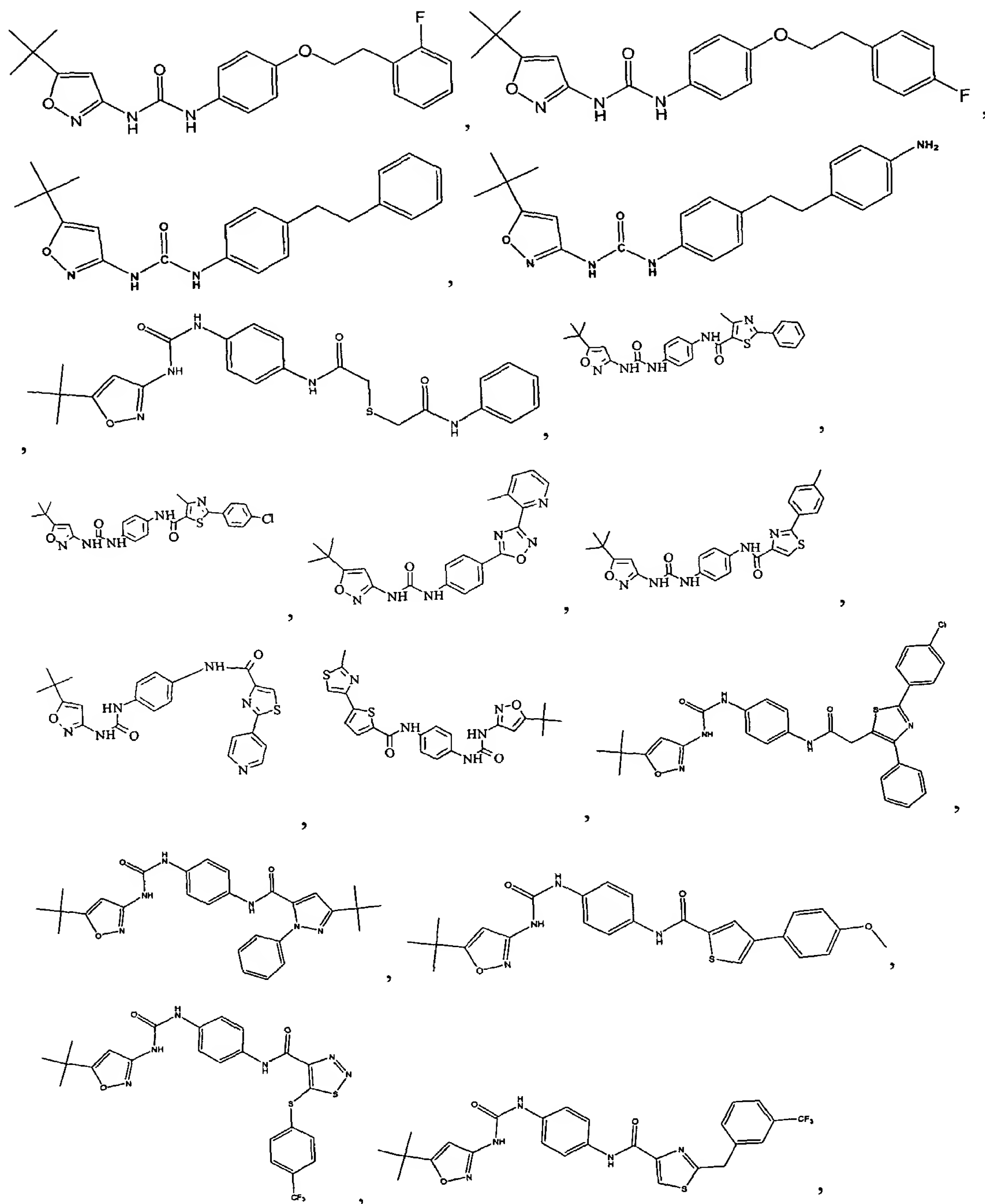


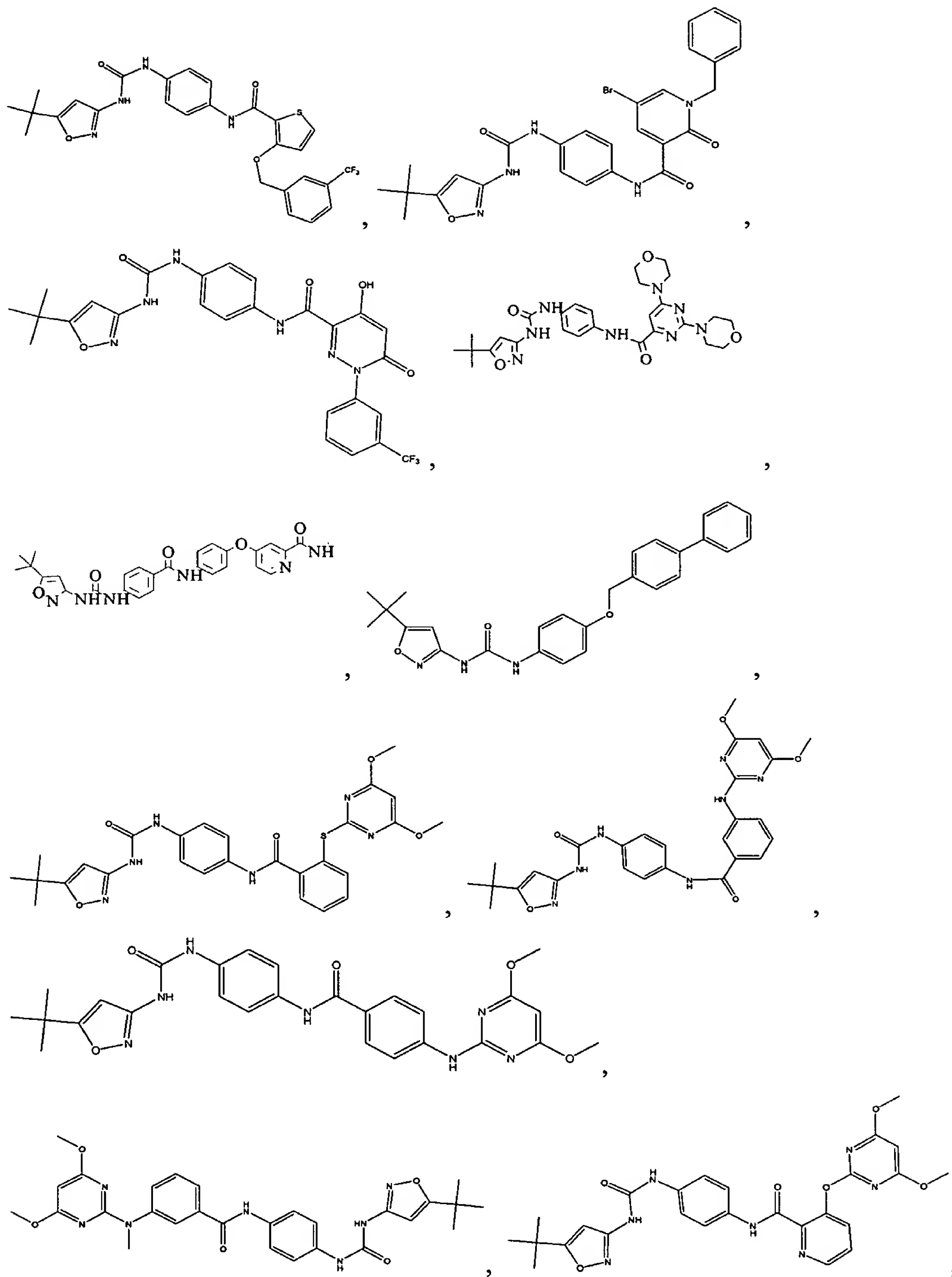


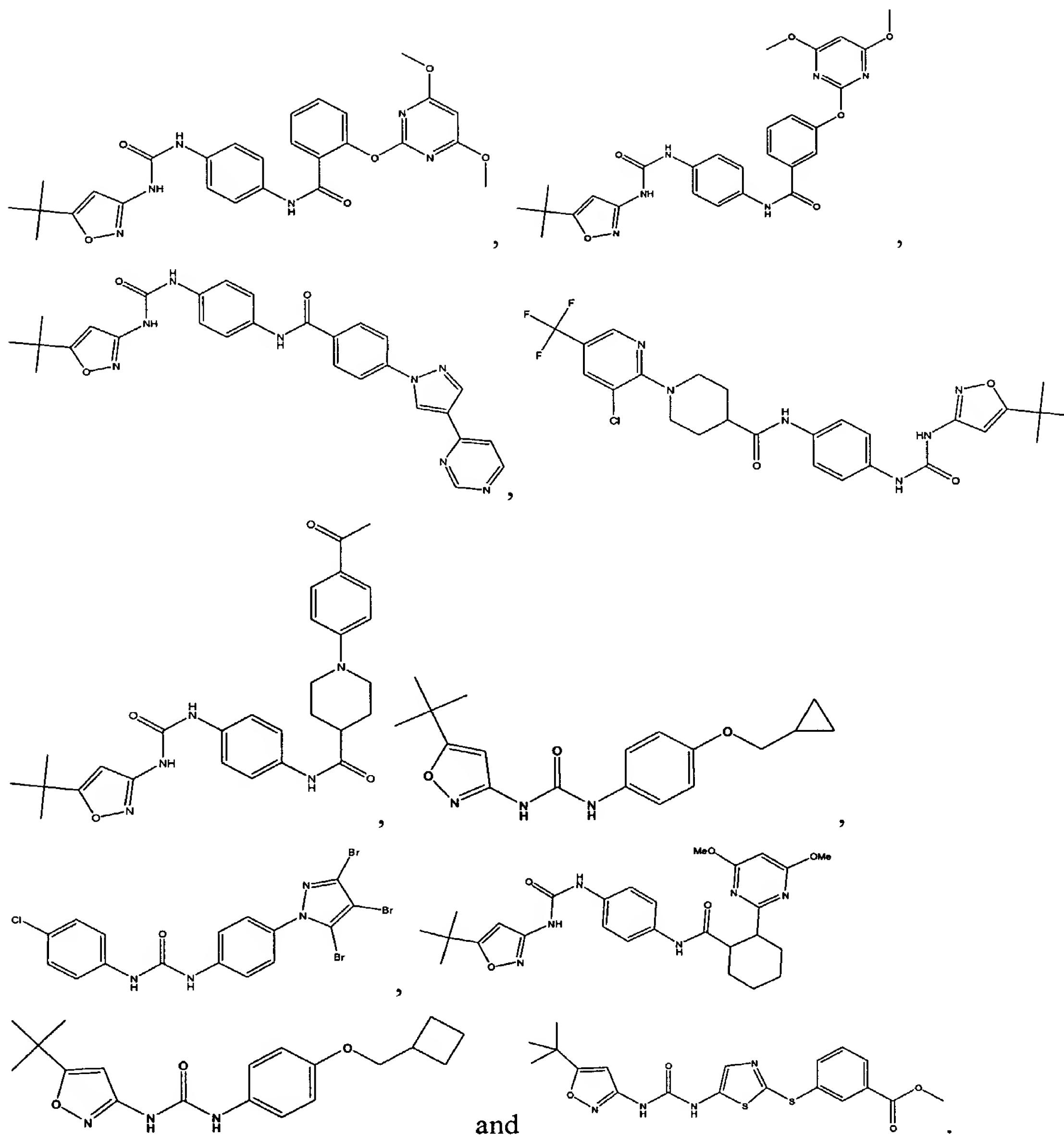






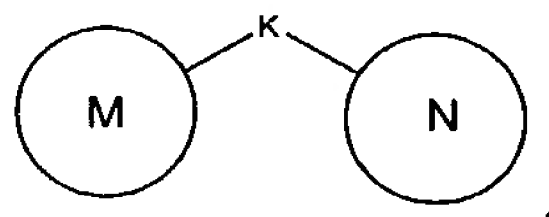




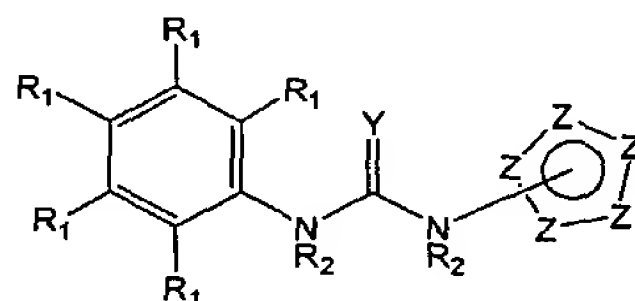


Exemplary p38 Modulators

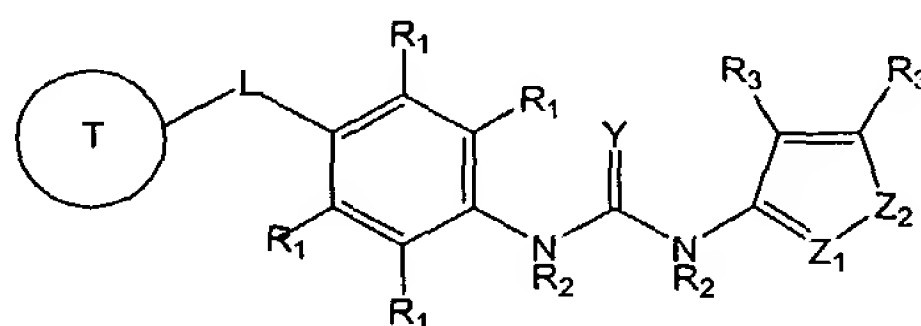
Methods for modulating p38 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:



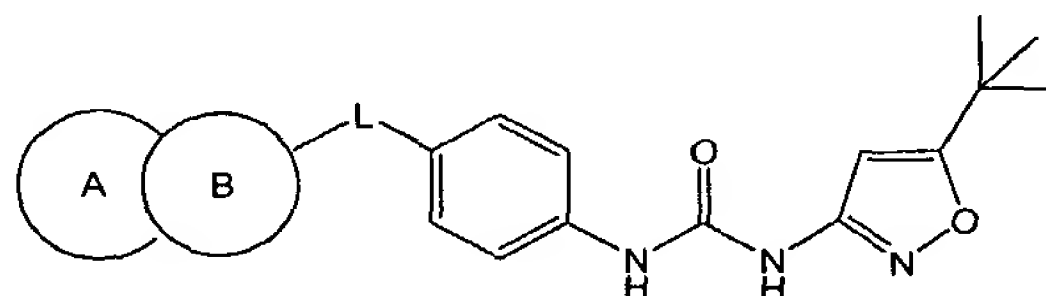
Methods for modulating p38 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:



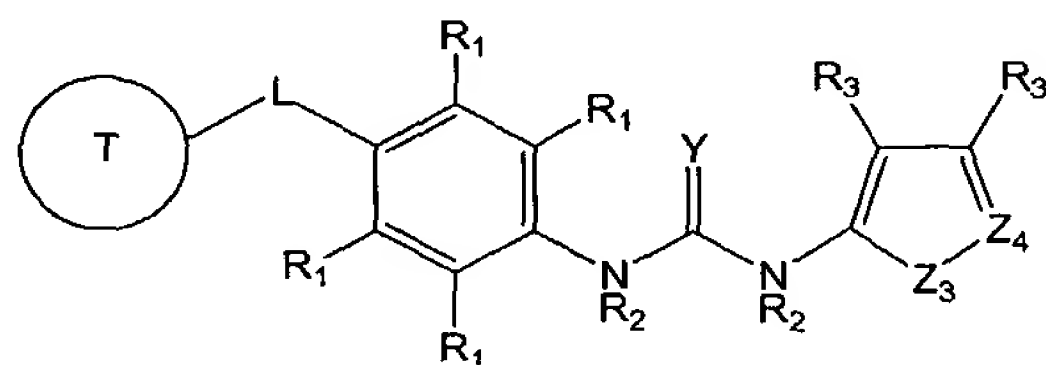
5 Methods for modulating p38 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:



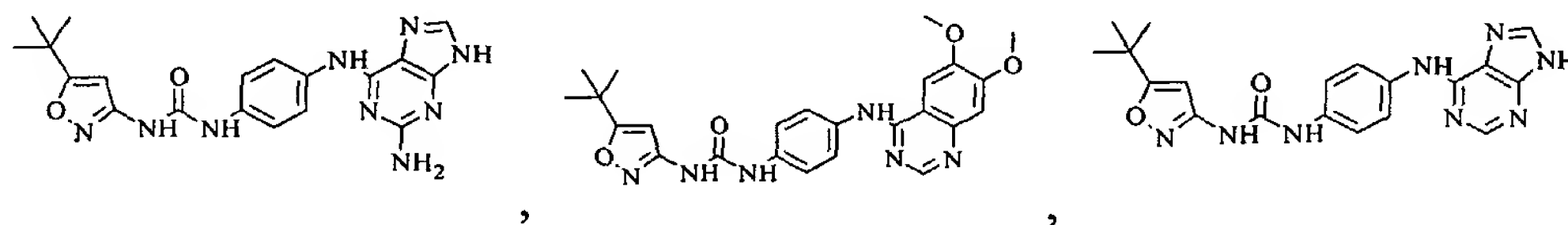
Methods for modulating p38 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:

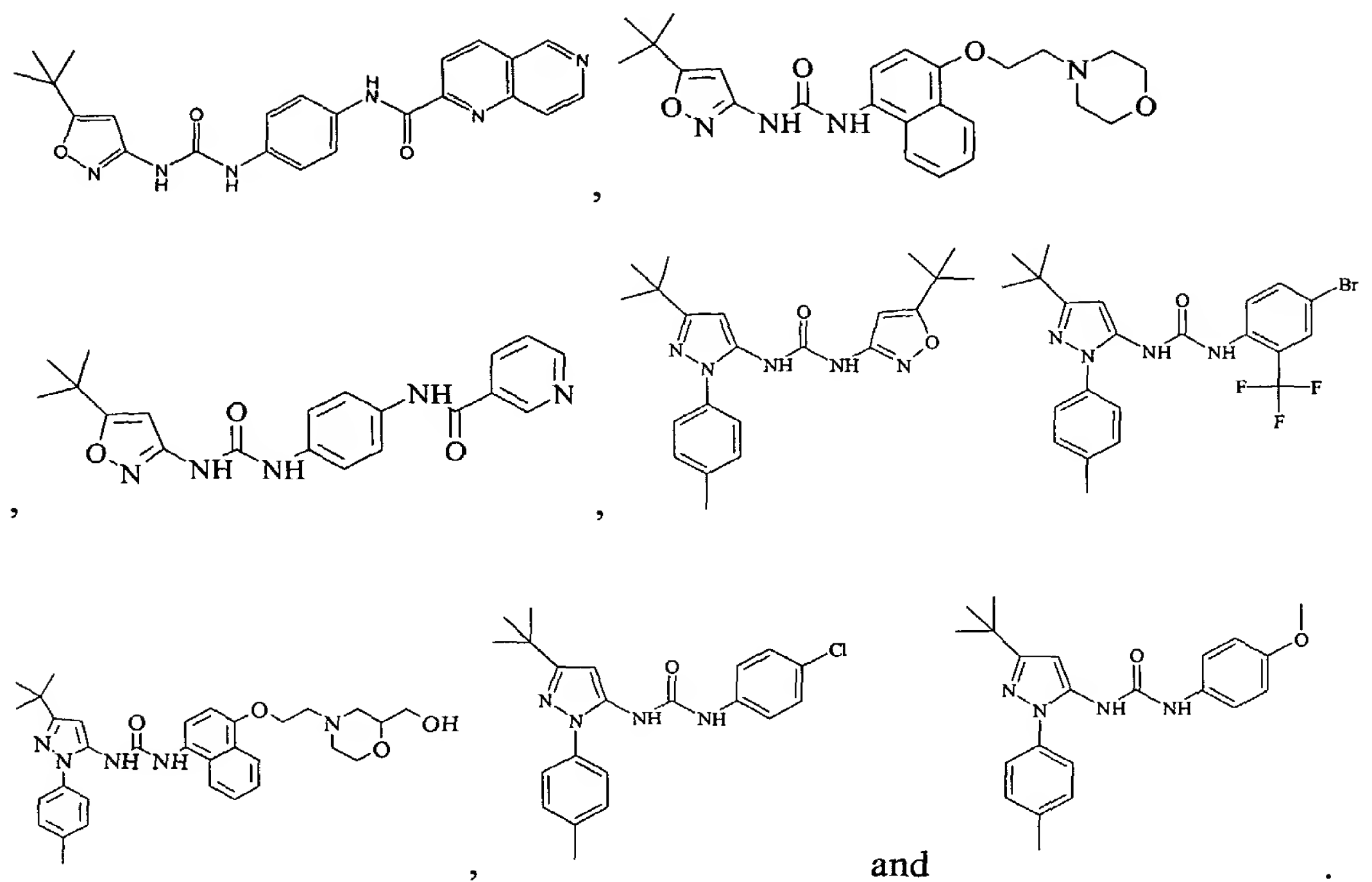


10 Methods for modulating p38 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:



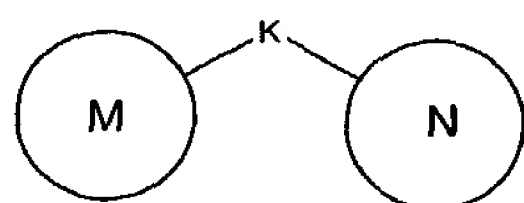
15 Provided herein are methods for modulating p38 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of a compound selected from the group consisting of:



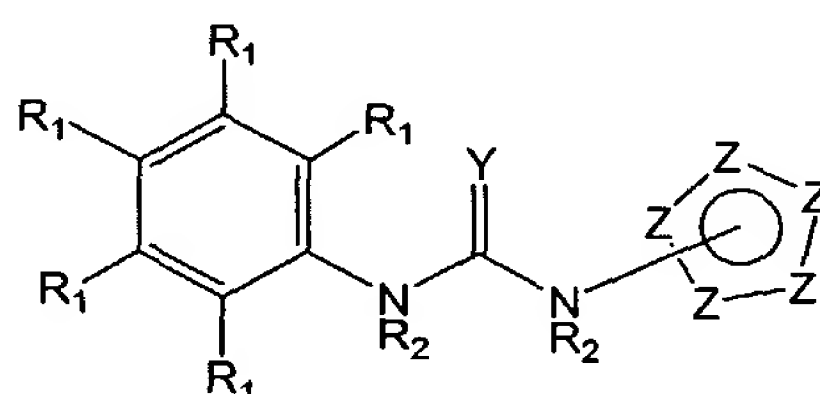


5 Exemplary MKNK2 Modulators

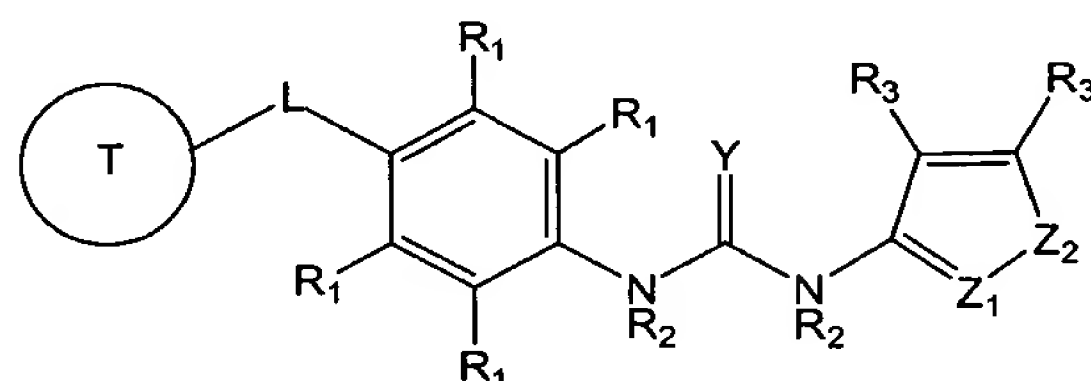
Methods for modulating MKNK2 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:



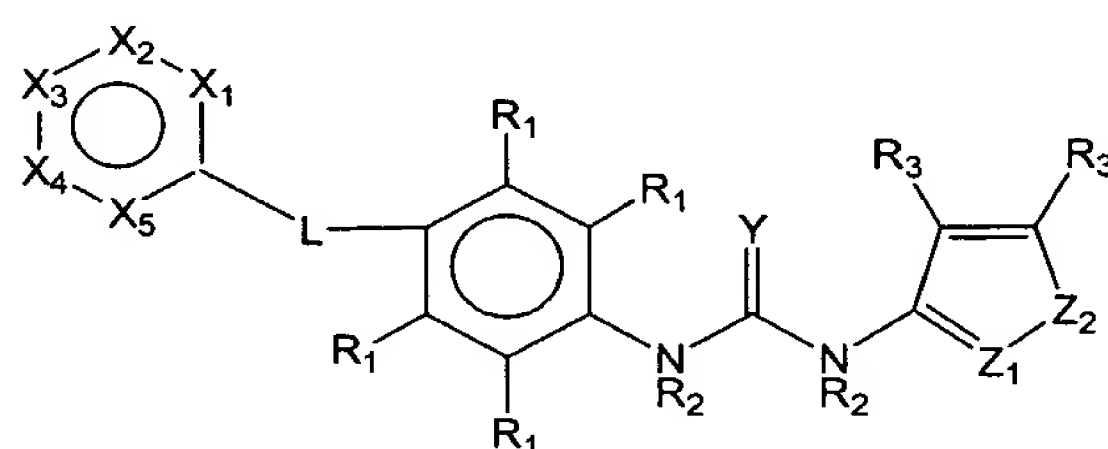
10 Methods for modulating MKNK2 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:



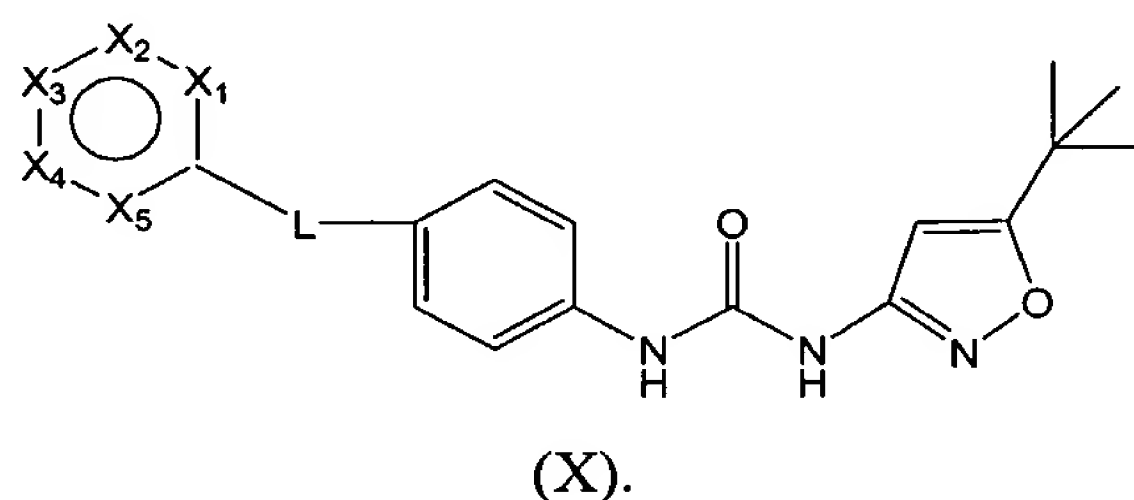
Methods for modulating MKNK2 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:



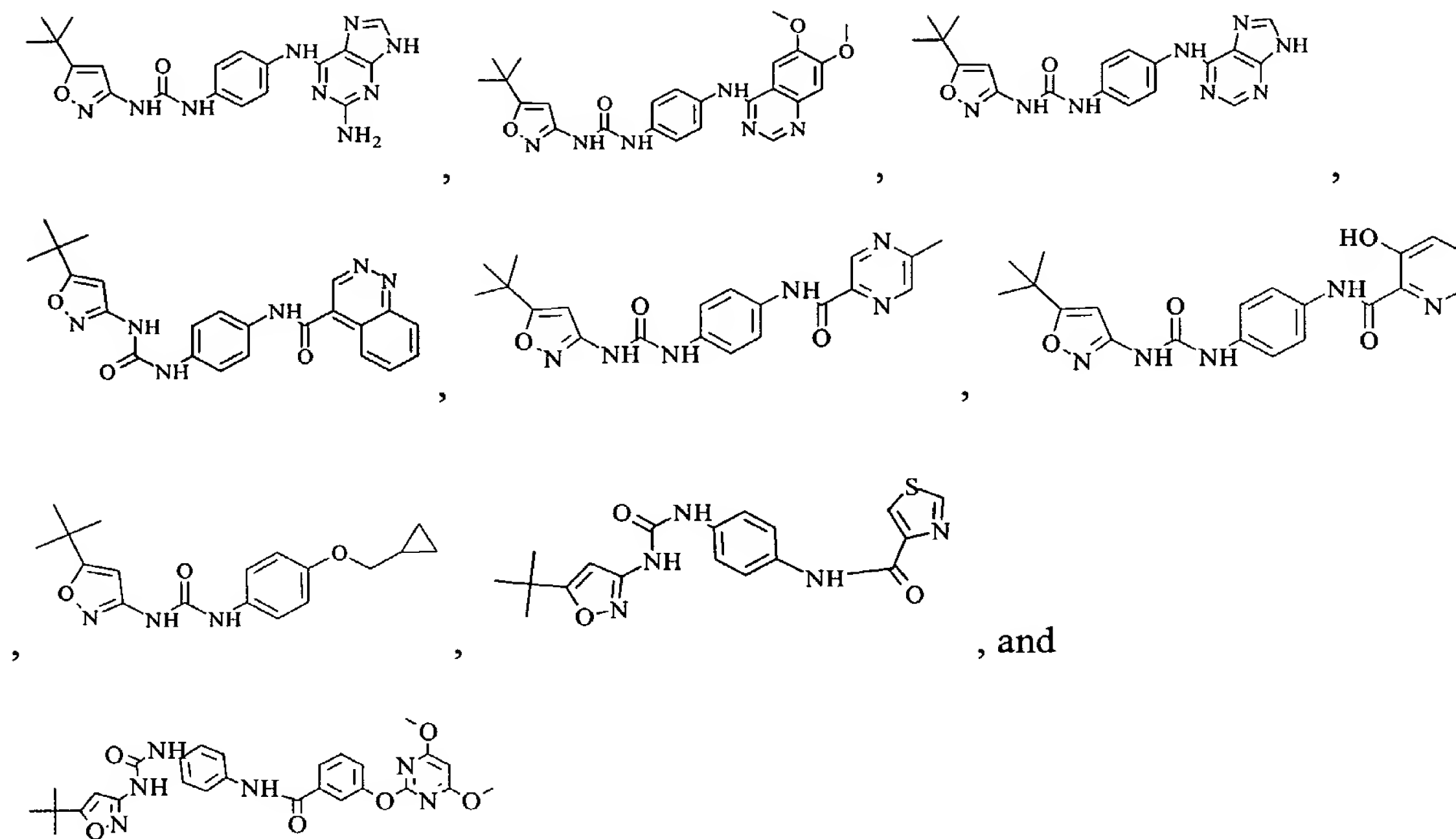
5 Methods for modulating MKNK2 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:



10 Methods for modulating MKNK2 kinase, said method comprising administering an effective amount of a compound corresponding to the following structure are provided herein:

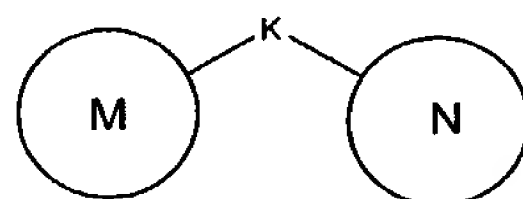


15 Provided herein are methods for modulating MKNK2 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:

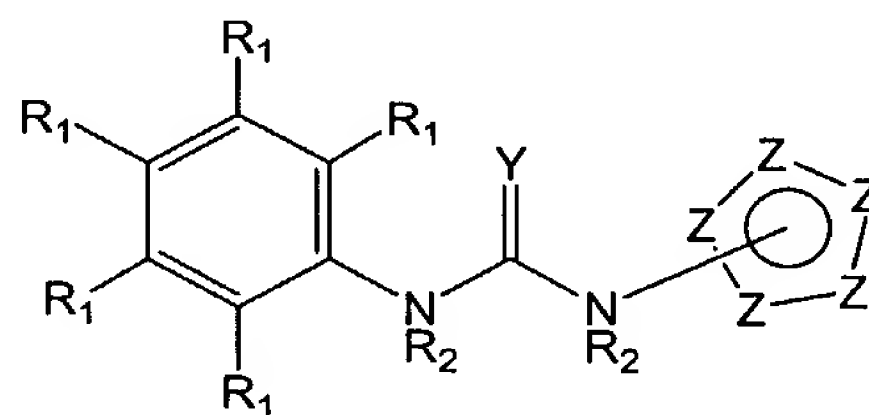


5 Exemplary STK10 Modulators

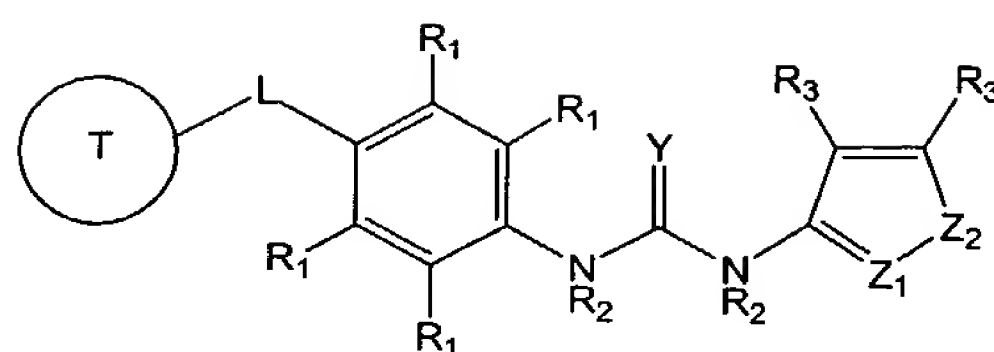
Methods for modulating STK10 kinase, said method comprising administering an effective amount of a compound of the following structure are provided herein:



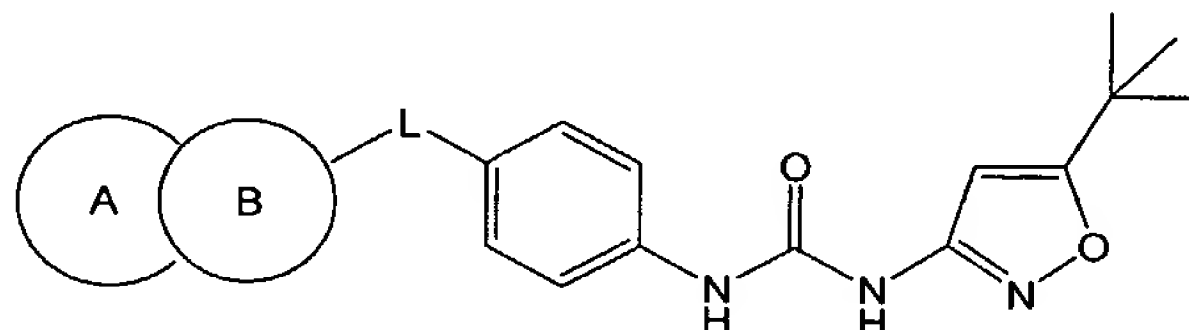
10 Methods for modulating STK10 kinase, said method comprising administering an effective amount of a compound of the following structure are provided herein:



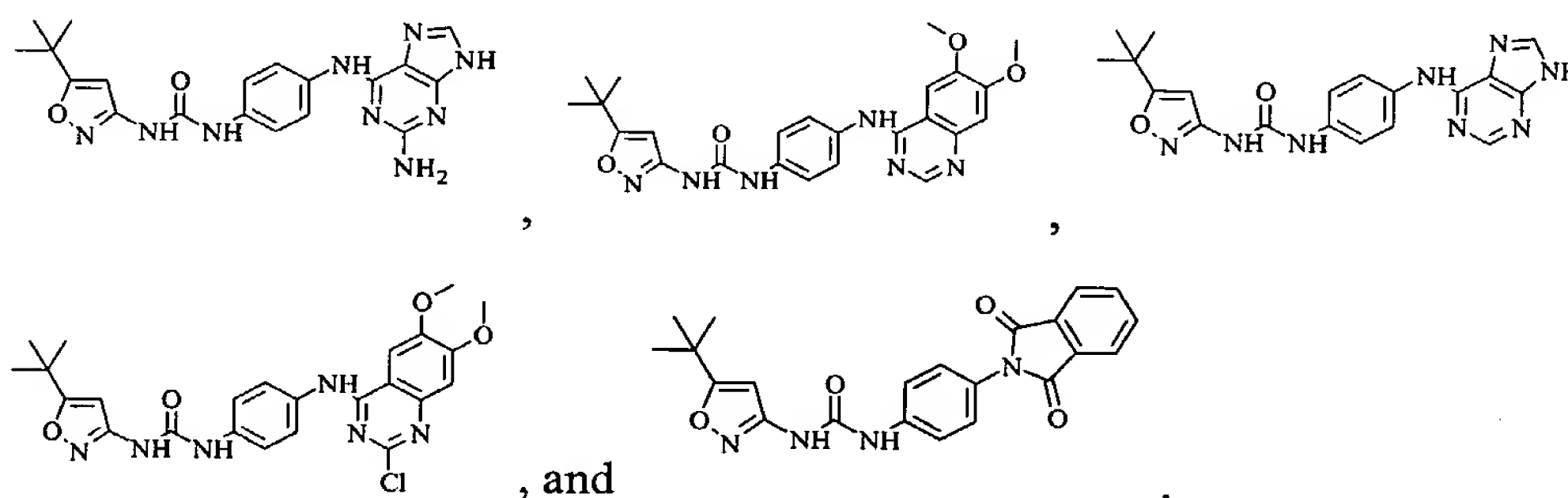
Methods for modulating STK10 kinase, said method comprising administering an effective amount of a compound of the following structure are provided herein:



Methods for modulating STK10 kinase, said method comprising administering an effective amount of a compound of the following structure are provided herein:



5 Provided herein are methods for modulating STK10 kinase, said method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of a compound selected from the group consisting of:



10 In some embodiments, the protein kinase is selected from the group comprising Ste (sterile 20, sterile 11 and sterile 7); camk (calmodulin regulated kinases and related kinases); AGC (protein kinase A, protein kinase G and protein kinase C) and CMGC (cdk, map kinase, glycogen synthetase kinase and clk). The sterile 20 kinases include, for example, PAK and CZ.

15 In some embodiments, the protein tyrosine kinase is selected from the "HER" receptor tyrosine kinase subfamily, which includes EGFR (epithelial growth factor receptor), HER2, HER3 and HER4. In further embodiments, the protein tyrosine kinase is selected from the subfamily consisting of insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and insulin receptor related receptor (IRR).

In some embodiments, the protein tyrosine kinase is selected from the platelet derived growth factor receptor (PDGFR) subfamily, which includes PDGFR α , PDGFR β , CSFIR, c-kit and c-fms. In another embodiment, the protein tyrosine kinase is the vascular endothelial growth factor ("VEGF") receptor subgroup.

5 In some embodiments, the protein tyrosine kinase is selected from the fetus liver kinase ("flk") receptor subfamily, which includes kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1), flk-1R, flk-4 and fms-like tyrosine kinase 1 (flt-1). In further embodiments, the protein tyrosine kinase is selected from the fibroblast growth factor ("FGF") receptor subgroup, which includes the receptors FGFR1, FGFR 2, FGFR3, and FGFR4, and the
10 ligands, FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, and FGF7. In a still further embodiment, the protein tyrosine kinase is the tyrosine kinase growth factor receptor family, c-Met. In some embodiments, the protein tyrosine kinase is an fms-like tyrosine kinase 3 receptor kinase (FLT-3 kinase).

The present invention provides compounds which modulate the activity, and in some
15 embodiments, preferentially inhibit non-receptor tyrosine kinases. In some embodiments, the non-receptor tyrosine kinases include Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack, their respective subfamilies. In a further embodiment, the non-receptor tyrosine kinase is selected from the Src subfamily, which includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

20 The compounds and compositions disclosed herein may be used for the prevention or treatment of cancers such as stomach, gastric, bone, ovary, colon, lung, brain, larynx, lymphatic system, genitourinary tract, ovarian, squamous cell carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, lung cancer, bladder cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, breast cancer, small-cell lung cancer, leukemia, glioma, colorectal cancer, genitourinary cancer gastrointestinal cancer, or pancreatic cancer.
25 In particular, the cancer is acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs).

30 Compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of an fms-like tyrosine kinase 3 (FLT-3) receptor modulating compound are provided herein. In one embodiment, the disease is cancer. In

other embodiments, the cancer is a malignant tumor, or a hematologic malignancy such as leukemia and lymphoma. In some embodiments, the leukemia is acute myelogenous leukemia (AML), a B-precursor cell acute lymphoblastic leukemia, myelodysplastic leukemia, T-cell acute lymphoblastic leukemia or chronic myelogenous leukemia (CML).

5 Compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a Stem Cell Factor (SCF), c-kit, receptor modulating compound are provided herein. In one embodiment, the disease is cancer. In other
embodiments, the cancer is a malignant tumor, or a hematologic malignancy such as
leukemia and lymphoma. In some embodiments, the cancer is small-cell lung cancer, or
10 breast cancer. In some embodiments, the leukemia is acute myelogenous leukemia (AML).
In some embodiments, the malignant tumor is a germ cell tumor, a mast cell tumor, a
gastrointestinal stromal tumor (GIST), melanoma, or a neuroblastoma.

Compositions and methods for treating a disease comprising administering to a subject in
need thereof an effective amount of a Bcr-Abl receptor modulating compound are provided
15 herein. In one embodiment, the disease is cancer. In other embodiments, the cancer is a
malignant tumor, or a hematologic malignancy such as leukemia and lymphoma. In some
embodiments, the leukemia is chronic myeloid leukemia (CML) or acute myelogenous
leukemia (AML).

Compositions and methods for treating a disease comprising administering to a subject in
need thereof an effective amount of a Platelet-Derived Growth Factor (PDGF) receptor
20 modulating compound are provided herein. In one embodiment, the disease is cancer. In
other embodiments, the cancer is a malignant tumor, or a hematologic malignancy such as
leukemia and lymphoma. In some embodiments, the leukemia is acute lymphoblastic
leukemia (ALL). In some embodiments, the lymphoma is T- cell lymphoma. In some
25 embodiments, the malignant tumor is melanoma, or glioblastoma. In a further embodiment,
the disease is a nonmalignant proliferation disease. In some embodiments, the nonmalignant
proliferation disease is atherosclerosis, or restenosis. In a still further embodiment, the
disease is a fibroproliferative disorder. In some embodiments, the fibroproliferative disorder
is obliterative bronchiolitis.

30 These and other aspects of the present invention will become evident upon reference to
the following detailed description. In addition, various references are set forth herein which

describe in more detail certain procedures or compositions, and are incorporated by reference in their entirety.

DISCLOSURE OF THE INVENTION

To more readily facilitate an understanding of the invention and its preferred
5 embodiments, the meanings of terms used herein will become apparent from the context of this specification in view of common usage of various terms and the explicit definitions of other terms provided in the glossary below or in the ensuing description.

Glossary of Terms

Unless otherwise stated, the following terms used in this application, including the
10 specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg (1992) “ADVANCED ORGANIC CHEMISTRY 3RD ED.” Vols. A and B, Plenum Press, New York. Unless otherwise
15 indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art are employed.

The term “modulator” means a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, agonist, antagonist, and the like.

20 The term “agonist” means a molecule such as a compound, a drug, an enzyme activator or a hormone that enhances the activity of another molecule or the activity of a receptor site either directly or indirectly.

The term “antagonist” means a molecule such as a compound, a drug, an enzyme inhibitor, or a hormone, that diminishes or prevents the action of another molecule or the
25 activity of a receptor site either directly or indirectly.

The terms “effective amount” or “therapeutically effective amount” refer to a sufficient amount of the agent to provide the desired biological result. That result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic use is
30 the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in a disease. An appropriate “effective” amount in

any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the terms “treat” or “treatment” are synonymous with the term “prevent” and are meant to indicate a postponement of development of diseases, preventing the development of diseases, and/or reducing severity of such symptoms that will or are expected to develop. Thus, these terms include ameliorating existing disease symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disorder or disease, e.g., arresting the development of the disorder or disease, relieving the disorder or disease, causing regression of the disorder or disease, relieving a condition caused by the disease or disorder, or stopping the symptoms of the disease or disorder.

By “pharmaceutically acceptable” or “pharmacologically acceptable” is meant a material which is not biologically or otherwise undesirable, i.e., the material may be administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

“Carrier materials” include any commonly used excipients in pharmaceuticals and should be selected on the basis of compatibility and the release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. “Pharmaceutically compatible carrier materials” may comprise, e.g., acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999).

As used herein, the term “subject” encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans,

non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like.

Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the present invention, the mammal is a human.

The term "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density,

hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

As used herein, the term “biological sample” is broadly defined to include any cell, tissue, organ or multicellular organism. A biological sample can be derived, for example, from cell or tissue cultures *in vitro*. Alternatively, a biological sample can be derived from a living organism or from a population of single cell organisms.

As used herein, the term “linker” means any divalent linking moiety used to connect, join, or attach two chemical groups. For example, linkers may be used to join two cyclic groups, such as to join two aryl groups (*e.g.*, phenyl), an aryl group to a cycloalkyl group, an aryl group to a heterocyclyl group, a cycloalkyl group to a cycloalkyl group, a cycloalkyl group to a heterocyclyl group, and the like. Representative linkers include, but are not limited to, a covalent bond, -(substituted or unsubstituted alkylene)-, -(substituted or unsubstituted alkenylene)-, -(substituted or unsubstituted alkynylene)-, -(substituted or unsubstituted cycloalkylene)-, -(substituted or unsubstituted heterocyclylene)-, -(substituted or unsubstituted arylene)-, and -(substituted or unsubstituted heteroarylene)-. Exemplary linkers also include -O-, -S-, -S(O)-, -S(O)₂-, -S(O)₃-, -C(O)-, -NH-, -N=, -N=N-, =N-N=, -C(O)NH-, -S(O)NH-, and the like. Additional examples of linkers include -O(substituted or unsubstituted alkylene)-, -N(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -C(O)(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-, -NHC(O)(substituted or unsubstituted alkenylene)-, and the like. Linkers, as represented herein, embrace divalent moieties in any chemically feasible directionality. For example, compounds comprising a linker-C(O)NH- which attaches two aryl groups, Ar₁ to Ar₂, include Ar₁-C(O)NH-Ar₂ as well as Ar₁-NHC(O)-Ar₂.

As used herein, the term “halogen” includes fluorine, chlorine, bromine, and iodine.

As used herein, “alkyl” means a straight chain or branched, saturated or unsaturated chain having from 1 to 10 carbon atoms. Representative saturated alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-

5 methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl, and longer alkyl groups, such as heptyl, and octyl. An alkyl group can be unsubstituted or substituted. Unsaturated alkyl groups include alkenyl groups and alkynyl groups, discussed below. Alkyl groups containing three or more carbon atoms may be straight, branched or cyclized.

As used herein, "lower alkyl" means an alkyl having from 1 to 5 carbon atoms.

10 As used herein, an "alkenyl group" includes a monovalent unbranched or branched hydrocarbon chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to, (C₂-C₈) alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted.

15 As used herein, "alkynyl group" includes a monovalent unbranched or branched hydrocarbon chain having one or more triple bonds therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkynyl groups include, but are not limited to, (C₂-C₆) alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl. An alkynyl group can be unsubstituted or substituted.

20 The terms "trifluoromethyl," "sulfonyl," and "carboxyl" include CF₃, SO₃H, and CO₂H, respectively.

The term "alkoxy" as used herein includes -O-(alkyl), wherein alkyl is defined above.

As used herein, "alkoxyalkoxy" includes -O-(alkyl)-O-(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

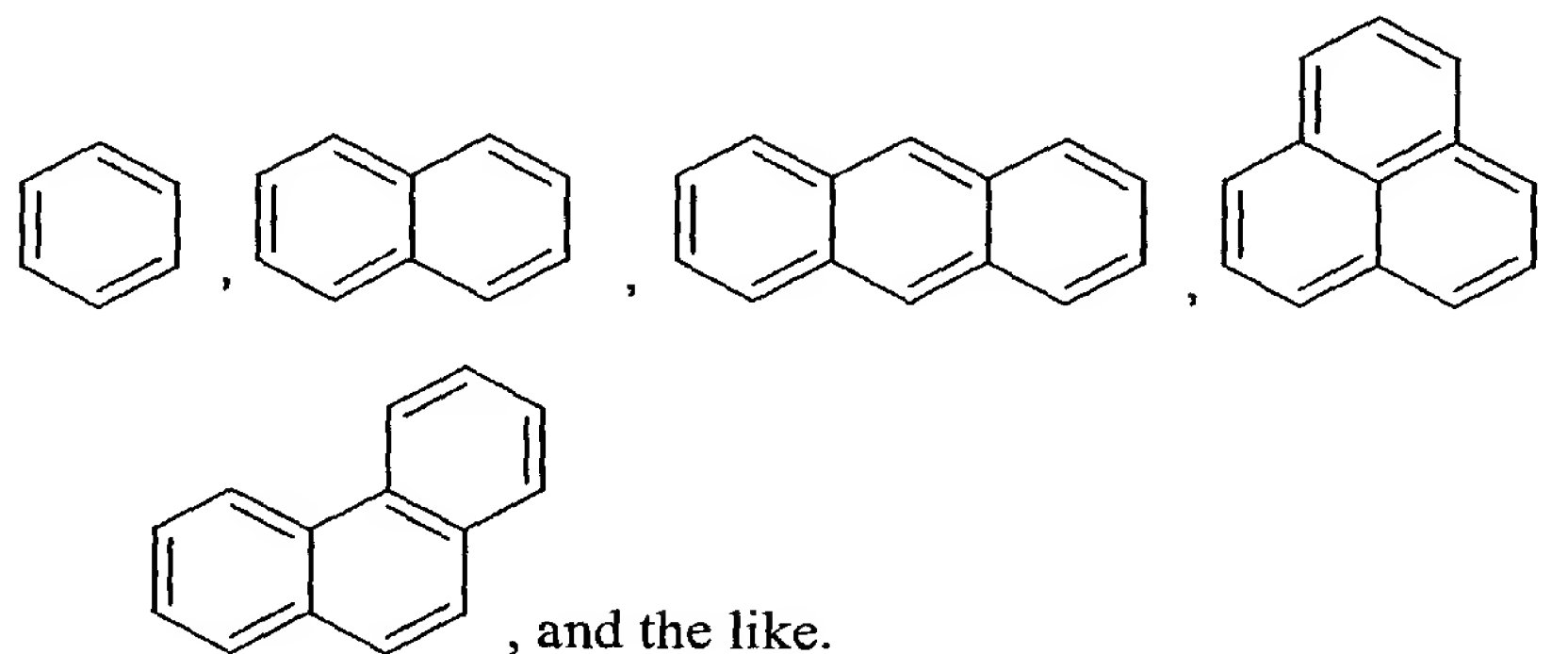
25 As used herein, "alkoxycarbonyl" includes -C(O)O-(alkyl), wherein alkyl is defined above.

As used herein, "alkoxycarbonylalkyl" includes -(alkyl)-C(O)O-(alkyl), wherein alkyl is defined above.

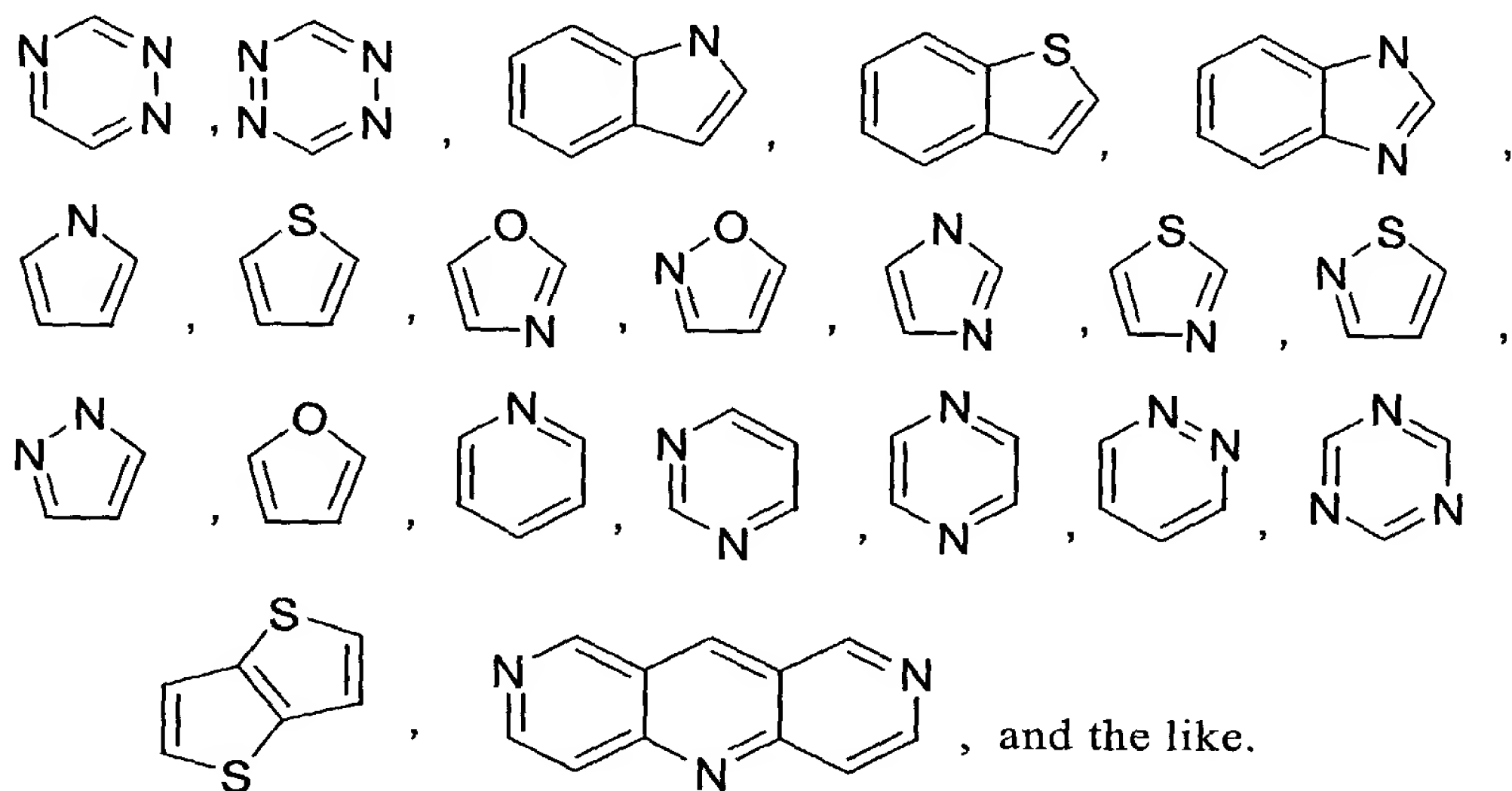
As used herein, "alkoxyalkyl" means -(alkyl)-O-(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

30 As used herein, the term "aryl" (Ar) refers to a monocyclic, or fused or spiro polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) having from 3 to 12

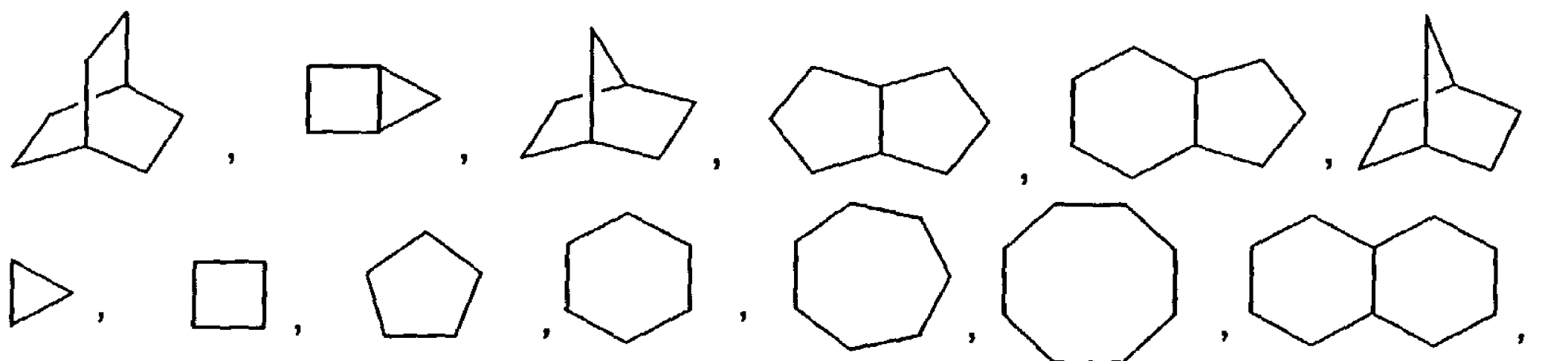
ring atoms per ring. Illustrative examples of aryl groups include the following moieties:

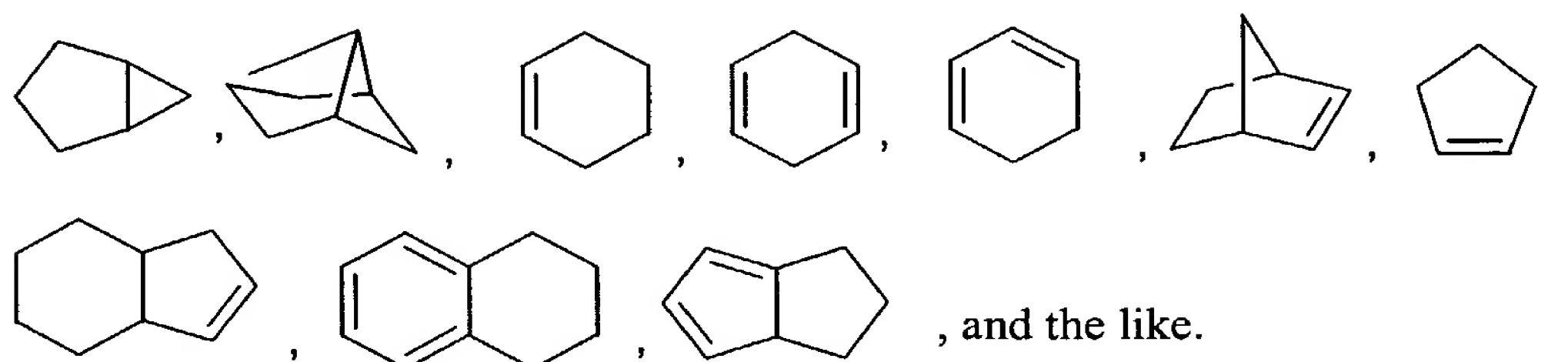


As used herein, the term “heteroaryl” (heteroAr) refers to a monocyclic, or fused or spiro polycyclic, aromatic heterocycle (ring structure having ring atoms selected from carbon atoms as well as nitrogen, oxygen, and sulfur heteroatoms) having from 3 to 12 ring atoms per ring. Illustrative examples of aryl groups include the following moieties:

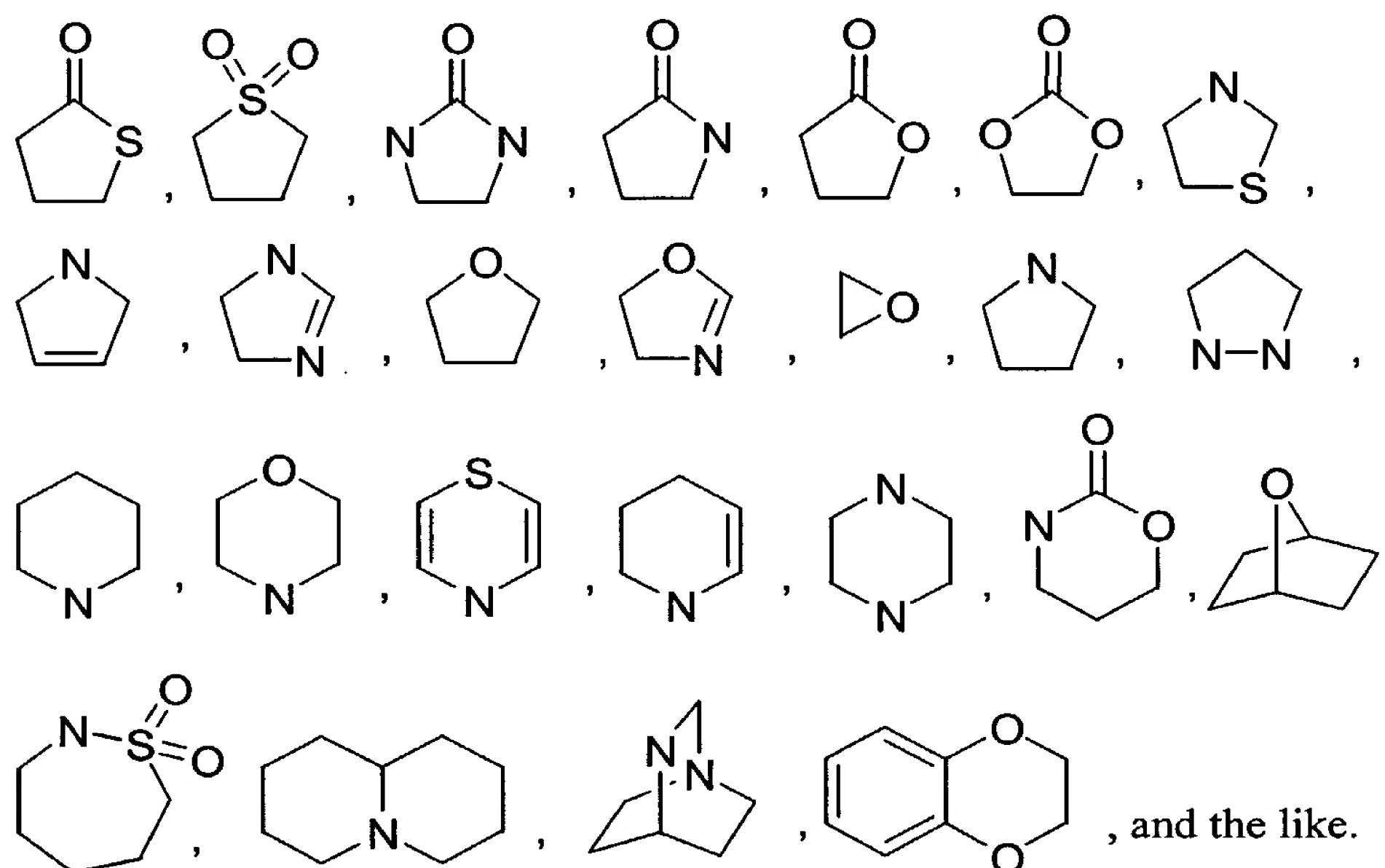


As used herein, the term “cycloalkyl” refers to a saturated or partially saturated, monocyclic or fused or spiro polycyclic, carbocycle having from 3 to 12 ring atoms per ring. Illustrative examples of cycloalkyl groups include the following moieties:





As used herein, the term “heterocycloalkyl” refers to a monocyclic, or fused or spiro polycyclic, ring structure that is saturated or partially saturated and has from 3 to 12 ring atoms per ring selected from C atoms and N, O, and S heteroatoms. Illustrative examples of heterocycloalkyl groups include:



As used herein, “aryloxy” includes -O-aryl group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or substituted.

As used herein, “arylalkyl” includes -(alkyl)-(aryl), wherein alkyl and aryl are defined above.

As used herein, “arylalkyloxy” includes -O-(alkyl)-(aryl), wherein alkyl and aryl are defined above.

As used herein, “cycloalkyl” includes a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon-carbon multiple bonds. Examples of cycloalkyl groups include, but are not limited to, (C₃-C₇)cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic

and bicyclic terpenes. A cycloalkyl group can be unsubstituted or substituted. Preferably, the cycloalkyl group is a monocyclic ring or bicyclic ring.

As used herein, "cycloalkyloxy" includes -O-(cycloalkyl), wherein cycloalkyl is defined above.

5 As used herein, "cycloalkylalkyloxy" includes -O-(alkyl)-(cycloalkyl), wherein cycloalkyl and alkyl are defined above.

As used herein, the term "alkylidene" includes the divalent radical --C_nH_{2n}--, wherein n is an integer from 1 to 8, such as --CH₂--, --CH₂CH₂--, --CH₂--CH₂--CH₂--, --CH₂CH₂CH₂CH₂--, --CH₂CH₂CH₂CH₂CH₂--, and the like, unsubstituted or substituted with one or more alkyl groups.

10 As used herein, "heteroatom-containing alkylidene" includes an alkylidene wherein at least one carbon atom is replaced by a heteroatom selected from nitrogen, oxygen, or sulfur, such as --CH₂CH₂OCH₂CH₂--, and the like, unsubstituted or substituted with one or more alkyl groups.

15 As used herein, "aminoalkoxy" includes --O-(alkyl)-NH₂, wherein alkyl is defined above.

As used herein, "mono-alkylamino" includes --NH(alkyl), wherein alkyl is defined above.

As used herein, "di-alkylamino" includes --N(alkyl)(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

20 As used herein, "mono-alkylaminoalkoxy" includes --O-(alkyl)-NH(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

As used herein, "di-alkylaminoalkoxy" includes --O-(alkyl)N(alkyl)(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

As used herein, "arylamino" includes --NH(aryl), wherein aryl is defined above.

25 As used herein, "arylalkylamino" includes --NH-(alkyl)-(aryl), wherein alkyl and aryl are defined above.

As used herein, "alkylamino" includes --NH(alkyl), wherein alkyl is defined above.

As used herein, "cycloalkylamino" includes --NH-(cycloalkyl), wherein cyclohexyl is defined above.

30 As used herein, "cycloalkylalkylamino" includes --NH-(alkyl)-(cycloalkyl), wherein alkyl and cycloalkyl are defined above.

As used herein, "aminoalkyl" includes $-(\text{alkyl})-\text{NH}_2$, wherein alkyl is defined above.

As used herein, "mono-alkylaminoalkyl" includes $-(\text{alkyl})-\text{NH}(\text{alkyl})$, wherein each "alkyl" is independently an alkyl group defined above.

As used herein, "di-alkylaminoalkyl" includes $-(\text{alkyl})-\text{N}(\text{alkyl})(\text{alkyl})$, wherein each "alkyl" is independently an alkyl group defined above.

The term "whole integer" is intended to include whole numbers. For example, a whole integer from 0 to 4 would include 0, 1, 2, 3, and 4.

Sulfonyl refers to the presence of a sulfur atom, which is optionally linked to another moiety such as an aliphatic group, an aromatic group, an aryl group, an alicyclic group, or a heterocyclic group. Aryl or alkyl sulfonyl moieties have the formula $-\text{SO}_2\text{R}_d$, and alkoxy moieties have the formula $-\text{O}-\text{R}_d$, wherein R_d is alkyl, as defined above, or is aryl wherein aryl is phenyl, optionally substituted with 1-3 substituents independently selected from halo (fluoro, chloro, bromo or iodo), lower alkyl (1-6C) and lower alkoxy (1-6C).

As used herein, the term "substituted" means that the specified group or moiety bears one or more suitable substituents.

As used herein, the term "unsubstituted" means that the specified group bears no substituents.

As used herein, the term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

Molecular embodiments of the present invention may possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are

not limited to moieties described in Patini et al., Chem, Rev, 1996, 96, 3147-3176 and references cited therein.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

To more readily facilitate an understanding of the invention and its preferred embodiments, the meanings of terms used herein will become apparent from the context of this specification in view of common usage of various terms and the explicit definitions of other terms provided in the glossary below or in the ensuing description.

Compounds

In one aspect, the present invention is directed to compounds, compositions, and methods for treating conditions associated with abnormal kinase activity. In one embodiment, compounds useful in the invention are derivatives of isoxazoles, pyrazoles and isothiazoles.

When the compounds of the invention contain one or more chiral centers, the invention includes optically pure forms as well as mixtures of stereoisomers or enantiomers.

Thus, the invention provides methods for modulating various kinases by providing an effective amount of a compound of the formulas described herein.

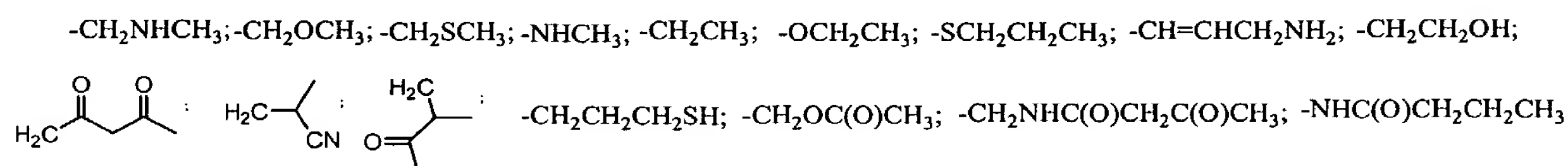
Salts of the compounds may be used for therapeutic and prophylactic purposes, where the salt is preferably a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example Q-toluenesulphonic, acids.

A "prodrug" refers to a drug or compound in which the pharmacological action results from conversion by metabolic processes within the body. Prodrugs are generally drug precursors that, following administration to a subject and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by a metabolic pathway. Some prodrugs have a chemical group present on the prodrug that renders it less active and/or confers solubility or some other property to the drug. Once the chemical group has been cleaved and/or modified from the prodrug the active drug is

generated. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. Additionally, prodrugs can increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent. See, e.g., Fedorak et al., *Am. J. Physiol.*, 269:G210-218 (1995);
 5 McLoed et al., *Gastroenterol.*, 106:405-413 (1994); Hochhaus et al., *Biomed. Chrom.*, 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics*, 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula et al., *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American
 10 Pharmaceutical Association and Pergamon Press, 1987. Prodrug forms of the above described compounds, wherein the prodrug is metabolized in vivo to produce a derivative as set forth above are included within the scope of the claims. Indeed, some of the above-described derivatives may be a prodrug for another derivative or active compound. The invention further provides for the optical isomers of the compounds disclosed herein,
 15 especially those resulting from the chiral carbon atoms in the molecule. In additional embodiments of the invention, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion may also be useful for the applications described herein.

In another aspect, compositions containing the above described analogs and derivatives
 20 are provided. Preferably, the compositions are formulated to be suitable for pharmaceutical or clinical use by the inclusion of appropriate carriers or excipients.

Groups such as carbonyl, carboxyl, alkoxy, amino, and cyano groups, etc., as shown in the formula above, need not be directly bound to the para position; they may be included elsewhere in the alkyl, alkenyl or alkynyl substituent. Thus, also acceptable substituents are
 25 the following representative forms:



each of which may further be substituted with a cycloalkyl, heterocycloalkyl, aryl or heteroaryl group.

30 It will also be evident that these substituents include, for example, trifluoromethyl,

difluoromethyl and fluoromethyl (alkyl substituted by halo) and trifluoromethoxy, difluoromethoxy and fluoromethoxy (alkyl where one carbon is replaced by O and is further substituted by halo).

Compounds of the invention which contain carboxyl groups or which contain amino groups may be supplied in the forms of their pharmaceutically acceptable salts.

Pharmaceutically acceptable salts of carboxylic acids include inorganic salts such as salts of sodium, potassium, calcium, magnesium and the like or salts formed with organic bases such as caffeine. Salts of amines are acid addition salts formed from inorganic acids such as hydrochloric, sulfuric, phosphoric acids or may be salts of organic acids such as acetates, maleates, propionates, and the like.

The invention also provides prodrug forms of the compounds described herein, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth above. Indeed, some of the above described derivatives may be a prodrug for another derivative or active compound. The invention further provides for the optical isomers of the compounds disclosed herein, especially those resulting from the chiral carbon atoms in the molecule. In additional embodiments of the invention, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are provided.

In another aspect of the invention, compositions containing the above described analogs and derivatives are provided. Preferably, the compositions are formulated to be suitable for pharmaceutical or clinical use by the inclusion of appropriate carriers or excipients.

In yet another aspect of the invention, pharmaceutical formulations are provided comprising at least one compound described above, or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

The compounds of the invention, especially when used in the invention methods and compositions, may be "conjugated" -that is they may be coupled to additional moieties that do not destroy their ability to modulate kinases. For example, the compounds might be coupled to a label such as a radioactive label, a fluorescent label and the like, or may be coupled to targeting agents such as antibodies or fragments, or to fragments to aid purification such as FLAG or a histidine tag. The compounds may also be coupled to specific binding partners such as biotin for use in assay procedures or to moieties that alter their

biological half-lives such as polyethylene glycol. Thus, the methods of the invention employ the invention compounds *per se* as well as conjugates thereof.

Synthesis of Compounds

Compounds of the present invention may be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in combination with methods described herein. *See, e.g.*, March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 3rd Ed., Vols. A and B (Plenum 1992), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 2nd Ed. (Wiley 1991). General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein.

The compounds of the invention are synthesized by methods well known in the art. The compounds of the invention are ureas or cyclic forms thereof and can be synthesized using generally known procedures for urea synthesis.

In one group of methods, an amine is reacted with an isocyanate in an aprotic solvent. Typically, in some embodiments, a molar excess of the amine is used in the presence of an aprotic solvent and the reaction is conducted at room temperature. The reaction mixture is then poured into water and precipitated with salt to recover the crude product which is then purified according to standard methods.

In alternative methods, the ureas are formed from two separate amine reactants in the presence of a condensing agent such as 1,1-carbonyldiimidazole (CDI) in the presence of an inert nonpolar solvent such as dichloromethane. One of the amines is first added to a solution of CDI in solvent under cooling conditions and then stirred at room temperature with the other amine. After removal of solvent, the crude product can be purified using standard procedures.

In still another method, one of the amines is added in an aprotic solvent to a solution of triphosgene and then treated with the other amine reactant dissolved in an inert solvent in the presence of base such as triethylamine. After reaction at room temperature, the mixture may be diluted with, for example, ethylacetate and washed with water and brine, dried and

purified.

In still another method, one of the amine components is treated with 4-nitrophenylchloroformate in the presence of mild base in a solvent such as N-methylpyrrolidone (NMP). The other amine is then added and the reaction mixture heated, then cooled, poured into water, extracted into chloroform and further purified.

Alternatively, the urea may be formed by the reaction of an amine with the counterpart halo acylamine which is formed from the parent amine by treatment with phosgene and base in an inert solvent such as methylene dichloride or by reacting an amine with its counterpart amine with an acyl amine containing an alternate leaving group formed by reaction of that amine with 4-nitrophenylchloroformate in the presence of an amine base and in an inert solvent.

Details of these methods can be found in Matsuno *et al. J. Med. Chem.* 45:3057-66 (2002); Matsuno *et al. J. Med. Chem.* 45:4513-23 (2002); and Pandley *et al., J. Med. Chem.* 45:3772-93 (2002).

Cyclized forms of the ureas may be obtained by treating the formed urea with dibromo derivatives of the bridge, typically in the presence of a strong base and in an inert aprotic polar solvent.

The ureas may be converted to thioureas by treating with Lawesson's reagent in the presence of toluene.

For compounds having the moiety $\text{Ar}^1\text{-L-Ar}^2$ is obtained by first protecting the amino group of p-hydroxy aniline destined to become Ar^1 with a protecting agent such as Boc and then coupling the hydroxy group of Ar^1 to an aryl alkyl halide. This coupling is conducted in the presence of strong base and in an aprotic solvent. After deprotection, the urea is formed by reaction with the isoxazole isocyanate. These techniques are exemplified below.

Selected examples of covalent linkages and precursor functional groups which yield them are given in the Table entitled "Examples of Covalent Linkages and Precursors Thereof." Precursor functional groups are shown as electrophilic groups and nucleophilic groups. The functional group on the organic substance may be attached directly, or attached via any useful spacer or linker as defined below.

Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
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Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	amines/anilines
Carboxamides	acyl azides	amines/anilines
Carboxamides	acyl halides	amines/anilines
Esters	acyl halides	alcohols/phenols
Esters	acyl nitriles	alcohols/phenols
Carboxamides	acyl nitriles	amines/anilines
Imines	Aldehydes	amines/anilines
Hydrazones	aldehydes or ketones	Hydrazines
Oximes	aldehydes or ketones	Hydroxylamines
Alkyl amines	alkyl halides	amines/anilines
Esters	alkyl halides	carboxylic acids
Thioethers	alkyl halides	Thiols
Ethers	alkyl halides	alcohols/phenols
Thioethers	alkyl sulfonates	Thiols
Esters	alkyl sulfonates	carboxylic acids
Ethers	alkyl sulfonates	alcohols/phenols
Esters	Anhydrides	alcohols/phenols
Carboxamides	Anhydrides	amines/anilines
Thiophenols	aryl halides	Thiols
Aryl amines	aryl halides	Amines
Thioethers	Azindines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	carboxylic acids	amines/anilines
Esters	carboxylic acids	Alcohols
hydrazines	Hydrazides	carboxylic acids
N-acylureas or Anhydrides	carbodiimides	carboxylic acids
Esters	diazoalkanes	carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	haloacetamides	Thiols
Ammotriazines	halotriazines	amines/anilines
Triazinyl ethers	halotriazines	alcohols/phenols
Amidines	imido esters	amines/anilines
Ureas	Isocyanates	amines/anilines
Urethanes	Isocyanates	alcohols/phenols
Thioureas	isothiocyanates	amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	phosphoramidites	Alcohols
Silyl ethers	silyl halides	Alcohols
Alkyl amines	sulfonate esters	amines/anilines
Thioethers	sulfonate esters	Thiols
Esters	sulfonate esters	carboxylic acids
Ethers	sulfonate esters	Alcohols
Sulfonamides	sulfonyl halides	amines/anilines
Sulfonate esters	sulfonyl halides	phenols/alcohols

In general, carbon electrophiles are susceptible to attack by complementary nucleophiles, including carbon nucleophiles, wherein an attacking nucleophile brings an electron pair to the carbon electrophile in order to form a new bond between the nucleophile and the carbon electrophile.

Suitable carbon nucleophiles include, but are not limited to alkyl, alkenyl, aryl and alkynyl Grignard, organolithium, organozinc, alkyl-, alkenyl, aryl- and alkynyl-tin reagents (organostannanes), alkyl-, alkenyl-, aryl- and alkynyl-borane reagents (organoboranes and organoboronates); these carbon nucleophiles have the advantage of being kinetically stable in water or polar organic solvents. Other carbon nucleophiles include phosphorus ylids, enol and enolate reagents; these carbon nucleophiles have the advantage of being relatively easy to generate from precursors well known to those skilled in the art of synthetic organic chemistry. Carbon nucleophiles, when used in conjunction with carbon electrophiles, engender new carbon-carbon bonds between the carbon nucleophile and carbon electrophile.

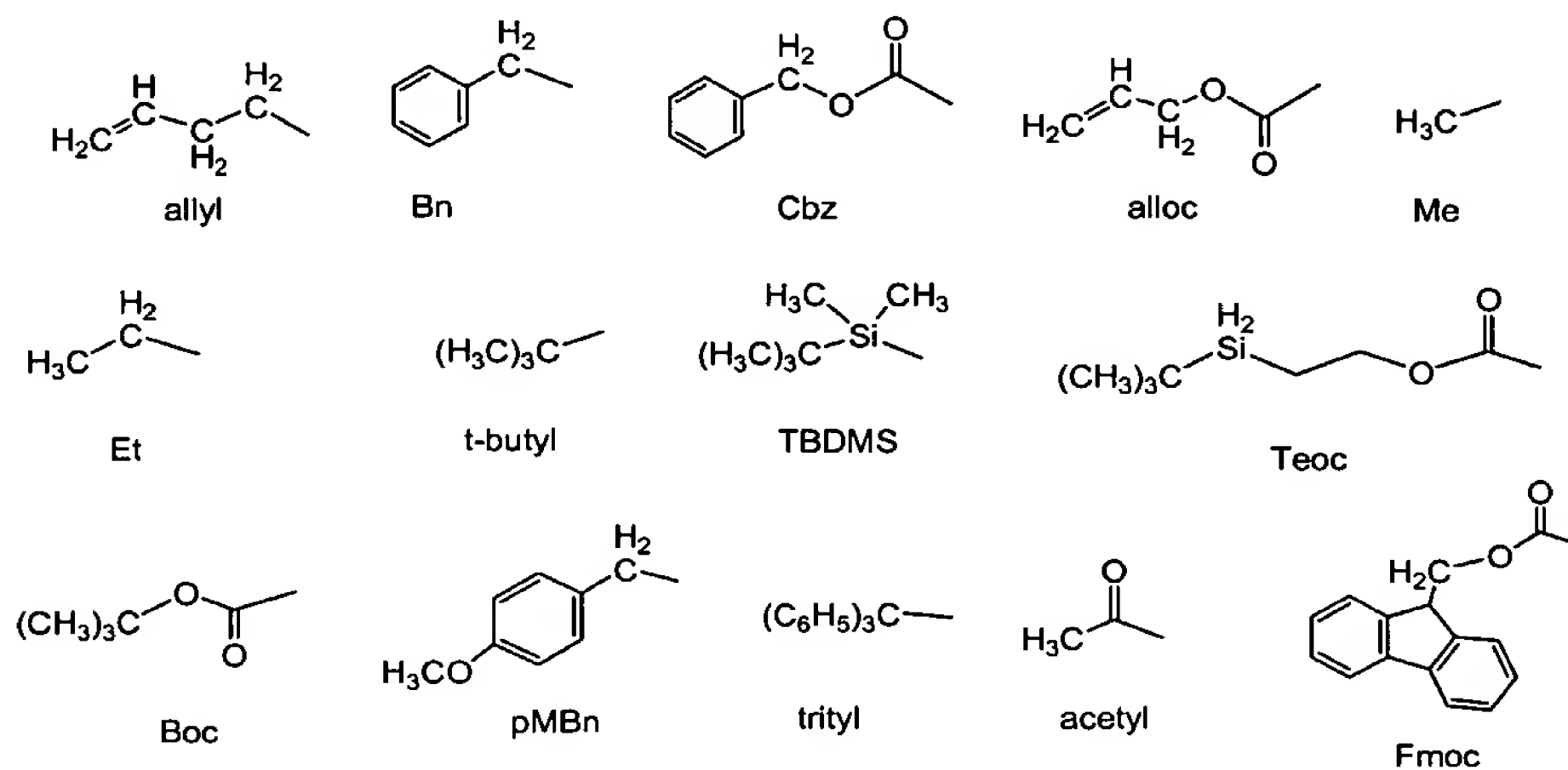
Non-carbon nucleophiles suitable for coupling to carbon electrophiles include but are not limited to primary and secondary amines, thiols, thiolates, and thioethers, alcohols, alkoxides, azides, semicarbazides, and the like. These non-carbon nucleophiles, when used in conjunction with carbon electrophiles, typically generate heteroatom linkages (C-X-C), wherein X is a heteroatom, e. g, oxygen or nitrogen.

The term "protecting group" refers to chemical moieties that block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. It is preferred that each protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. Protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester derivatives as exemplified herein, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd₀-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

Typically blocking/protecting groups may be selected from:



Other protecting groups are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

Biological Activity

Protein kinases (PKs) play a role in signal transduction pathways regulating a number of cellular functions, such as cell growth, differentiation, and cell death. PKs are enzymes that

5 catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. Abnormal PK activity has been related to disorders ranging from relatively non life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer). In addition, a variety of tumor types have dysfunctional growth factor
10 receptor tyrosine kinases, resulting in inappropriate mitogenic signaling. Protein kinases are believed to be involved in many different cellular signal transduction pathways. In particular, protein tyrosine kinases (PTK) are attractive targets in the search for therapeutic agents, not only for cancer, but also against many other diseases. Blocking or regulating the kinase phosphorylation process in a signaling cascade may help treat conditions such as cancer or inflammatory processes.

Protein tyrosine kinases are a family of tightly regulated enzymes, and the aberrant activation of various members of the family is one of the hallmarks of cancer. The protein-tyrosine kinase family includes Bcr-Abl tyrosine kinase, and can be divided into subgroups that have similar structural organization and sequence similarity within the kinase domain.

15 The members of the type III group of receptor tyrosine kinases include the platelet-derived growth factor (PDGF) receptors (PDGF receptors α and β), colony-stimulating factor (CSF-1) receptor (CSF-1R, c-Fms), FLT-3, and stem cell or steel factor receptor (c-kit).

The compounds, compositions, and methods provided herein are useful to modulate the activity of kinases including, but not limited to, ERBB2, ABL1, AURKA, CDK2, EGFR,
20 FGFR1, LCK, MAPK14, PDGFR, KDR, ABL1, BRAF, ERBB4, FLT3, KIT, and RAF1. In some embodiments, the compositions and methods provided herein modulate the activity of a mutant kinase.

Inhibition by the compounds provided herein can be determined using any suitable assay. In one embodiment, inhibition is determined in vitro. In a specific embodiment, inhibition is
25 assessed by phosphorylation assays. Any suitable phosphorylation assay can be employed. For example, membrane autophosphorylation assays, receptor autophosphorylation assays in intact cells, and ELISA's can be employed. See, e.g., Gazit, et al., J. Med. Chem. (1996) 39:2170-2177, Chapter 18 in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Ausubel, et al., eds. 2001). Cells useful in such assays include cells with wildtype or mutated forms. In one
30 embodiment, the wildtype is a kinase that is not constitutively active, but is activated with upon dimerization. For example, the mutant FLT3 kinase is constitutively active via internal

tandem duplication mutations or point mutations in the activation domain. Suitable cells include those derived through cell culture from patient samples as well as cells derived using routine molecular biology techniques, e.g., retroviral transduction, transfection, mutagenesis, etc. Exemplary cells include Ba/F3 or 32Dc13 cells transduced with, e.g., MSCV retroviral constructs FLT3-ITD (Kelly et al., 2002); Molm-13 and Molm14 cell line (Fujisaki Cell Center, Okayama, Japan); HL60 (AML-M3), AML193 (AML-M5), KG-1, KG-1a, CRL-1873, CRL-9591, and THP-1 (American Tissue Culture Collection, Bethesda, MD); or any suitable cell line derived from a patient with a hematopoietic malignancy.

In some embodiments, the compounds described herein significantly inhibit receptor tyrosine kinases. A significant inhibition of a receptor tyrosine kinase activity refers to an IC_{50} of less than or equal to 100 μ M. Preferably, the compound can inhibit activity with an IC_{50} of less than or equal to 50 μ M, more preferably less than or equal to 10 μ M, more preferably less than 1 μ M, or less than 100 nM, most preferably less than 50 nM. Lower IC_{50} 's are preferred because the IC_{50} provides an indication as to the in vivo effectiveness of the compound. Other factors known in the art, such as compound half-life, biodistribution, and toxicity should also be considered for therapeutic uses. Such factors may enable a compound with a lower IC_{50} to have greater in vivo efficacy than a compound having a higher IC_{50} . Preferably, a compound that inhibits activity is administered at a dose where the effective tyrosine phosphorylation, i.e., IC_{50} , is less than its cytotoxic effects, LD_{50} .

In some embodiments, the compounds selectively inhibit one or more kinases. Selective inhibition of a kinase, such as FLT3, p38 kinase, STK10, MKNK2, Bcr-Abl, c-kit, or PDGFR, is achieved by inhibiting activity of one kinase, while having an insignificant effect on other members of the superfamily.

c-kit

The Stem Cell Factor (SCF) receptor c-kit is a receptor protein tyrosine kinase that initiates cell growth and proliferation signal transduction cascades in response to SCF binding. c-kit is a 145-kD transmembrane glycoprotein and is the normal cellular homolog of the v-kit retroviral oncogene. It is also a member of the Type III transmembrane receptor protein tyrosine kinase subfamily, which includes the macrophage colony-stimulating factor-1 receptor, also known as the FMS receptor, the related FLT-3 receptor, and the platelet-derived growth factor (PDGF) α and β receptors. The c-kit gene product is expressed in

hematopoietic progenitor cells, mast cells, germ cells, interstitial cells of Cajal (ICC), and some human tumors. Inactivating mutations of c-kit or its ligand, Steel factor (SLF), have demonstrated that the normal functional activity of the c-kit gene product is essential for maintenance of normal hematopoiesis, melanogenesis, gametogenesis, and growth and differentiation of mast cells and ICC. SLF is produced by human and murine hematopoietic stromal cells, including endothelial cells, fibroblasts, and bone marrow-derived stromal cells.

In addition to its importance in normal cellular physiologic activities, c-kit plays a role in the biological aspects of certain human cancers, including germ cell tumors, mast cell tumors, gastrointestinal stromal tumors (GIST), small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia (AML), and neuroblastoma. Proliferation of tumor cell growth mediated by c-kit can occur by a specific mutation of the c-kit polypeptide that results in ligand independent activation or by autocrine stimulation of the receptor. In the former case, mutations that cause constitutive activation of c-kit kinase activity in the absence of SCF binding are implicated in malignant human cancers, including gastrointestinal stromal tumors, germ cell tumors, mast cell tumors, and myeloid leukemia's and in mastocytosis.

The activity of the c-kit receptor protein tyrosine kinase is regulated in normal cells, and as discussed the deregulated c-kit kinase activity is implicated in the pathogenesis of human cancers. In some types of tumors, inhibition of c-kit activity reduces cellular proliferation, suggesting a role for use of pharmacologic inhibitors of c-kit in the treatment of c-kit dependent malignancies.

In one embodiment, compositions and methods provided herein are effective to modulate the activity of c-kit. In other embodiments, compositions and methods provided herein are effective to selectively modulate the activity of c-kit.

Bcr-Abl

c-Abl is a nonreceptor tyrosine kinase that contributes to several leukogenic fusion proteins, including the deregulated tyrosine kinase, Bcr-Abl. Chronic myeloid leukemia (CML) is a clonal disease involving the pluripotent hematopoietic stem cell compartment and is associated with the Philadelphia chromosome [Nowell P. C. and Hungerford D. A. , Science 132,1497 (1960)], a reciprocal translocation between chromosomes 9 and 22 [(9:22) (q34; q11)] [Rowley J. D., Nature 243,290-293 (1973)]. The translocation links the c-Abl

tyrosine kinase oncogene on chromosome 9 to the 5' half of the bcr (breakpoint cluster region) gene on chromosome 22 and creates the fusion gene bcr/abl. The fusion gene produces a chimeric 8.5 kB transcript that codes for a 210-kD fusion protein (p210^{bcr-abl}), and this gene product is an activated protein tyrosine kinase. Thus, the Abelson tyrosine kinase is improperly activated by accidental fusion of the bcr gene with the gene encoding the intracellular non-receptor tyrosine kinase, c-Abl.

The Bcr domain interferes with the intramolecular Abl inhibitory loop and unveils a constitutive kinase activity that is absent in the normal Abl protein. Bcr-Abl tyrosine kinase is a potent inhibitor of apoptosis, and it is well accepted that the oncoprotein expresses a constitutive tyrosine kinase activity that is necessary for its cellular transforming activity. Constitutive activity of the fusion tyrosine kinase Bcr-Abl has been established as the characteristic molecular abnormality present in virtually all cases of chronic myeloid leukemia (CML) and up to 20 percent of adult acute lymphoblastic leukemia (ALL) [Faderl S. et al., N Engl J Med 341, 164-172 (1999); Sawyers C. L., N Engl J Med 340,1330-1340 (1999)].

Mutations present in the kinase domain of the Bcr-Abl gene of patients suffering from CML or Ph+ ALL account for the biological resistance of these patients towards STI571 treatment in that said mutations lead to resistance of the Bcr- Abl tyrosine kinase towards inhibition by STI571. Novel therapies for CML need to address this emerging problem of clinical resistance to STI571 (Gleevec). Because tumor progression in patients receiving STI571 seem to be mediated by amplification of or mutation in the Bcr-Abl gene that causes the tyrosine kinase to be less efficiently inhibited by the drug, newer tyrosine kinase inhibitors may be susceptible to the same mechanisms of resistance. None the less, these findings are extremely valuable in the development of new compounds or combinations of compounds which are capable to overcome resistance towards treatment with STI571. Furthermore, in view of the large number of protein kinase inhibitors and the multitude of proliferative and other PK-related diseases, there is an ever-existing need to provide novel classes of compounds that are useful as PK inhibitors and thus in the treatment of these PTK related diseases.

In one embodiment, compositions and methods provided herein are effective to modulate the activity of Bcr-Abl. In other embodiments, compositions and methods provided herein

are effective to selectively modulate the activity of Bcr-Abl. In a further embodiment, compositions of Formula G, e.g., compounds described in Examples M and O, inhibit the protein tyrosine kinase associated with mutated bcr-abl, which gives rise to observed clinical resistance towards treatment with STI571.

PDGFR

Platelet-Derived Growth factor Receptors (PDGFR's) are receptor tyrosine kinases that regulate proliferative and chemotatic responses. PDGFR's have two forms- PDGFR- α (CD140a) and PDGFR- β (CD140b). PDGFRs are normally found in connective tissue and glia but are lacking in most epithelia, and PDGF expression has been shown in a number of different solid tumors, from glioblastomas to prostate carcinomas. For instance, PDGFR kinases are involved in various cancers such as T- cell lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), melanoma, glioblastoma and others (see Bellamy W. T. et al. , Cancer Res. 1999,59, 728-733). In these various tumor types, the biological role of PDGF signaling can vary from autocrine stimulation of cancer cell growth to more subtle paracrine interactions involving adjacent stroma and angiogenesis. Furthermore, PDGF has been implicated in the pathogenesis of several nonmalignant proliferation diseases, including atherosclerosis, restenosis following vascular angioplasty and fibroproliferative disorders such as obliterative bronchiolitis. Therefore, inhibiting the PDGFR kinase activity with small molecules may interfere with tumor growth and angiogenesis.

The binding of PDGFR to its receptor activates the intracellular tyrosine kinase, resulting in the autophorylation of the receptor as well as other intracellular substrates such as Src, GTPase Activating Protein (GAP), and phosphatidylinositol-3-phosphate. Upon autophorylation the PDGFR also forms complexes with other signaling moieties including phospholipase C- γ (PLC- γ), phosphatidylinositol-3-kinase (PI3K), and raf-1. It appears to be involved in communication between endothelial cells and pericytes, a communication that is essential for normal blood vessel development.

It has been found previously that the disruption of the PDGFR- β in mice oblates neovascular pericytes that form part of the capillary wall. See Lindahl, P., *et al.*, *Science* (1997) 227:242-245; Hellstrom, M., *et al.*, *Development* (1999) 126:3047-3055. A recent study by Bergers, G., *et al.*, *J. Clin. Invest.* (2003) 111:1287-1295 has suggested that

inhibition of PDGFR kinase activity by certain compounds such as SU6668 or ST1571/Gleevec inhibits tumor growth and that these compounds combined with VEGFR inhibitor SU5416 were very effective in reducing tumor growth. Further, inhibition of PDGFR- β by Gleevec enhanced tumor chemotherapeutic efficacy in mice. Pietras, K., *et al.*, *Cancer Res.* (2002) 62:5476-5484. A review of PDGFR receptors as cancer drug targets by Pietras, K., *et al.*, appears in *Cancer Cell.* (2003) 3:439-443. Inhibition of this kinase activity is also effective where abnormal forms of PDGFR, such as the TEL/PDGFR- β fusion protein associated with chronic myelomonocytic leukemia (CMML) is produced. See also, Grisolan, J. L., *et al.*, *Proc. Natl. Acad. Sci. USA.* (2003) 100:9506-9511.

Inhibitors of PDGFR- β frequently also inhibit additional kinases involved in tumor growth such as BCR-ABL, TEL-ABL, and PDGFR- α . See, Carroll, M., *et al.*, *Blood* (1997) 90:4947-4952 and Cools, J., *et al.*, *Cancer Cell* (2003) 3:450-469. One class of established inhibitors of PDGFR kinase activity includes quinazoline derivatives which comprise piperazine substitutions. Such compounds are disclosed in Yu, J-C., *et al.*, *J. Pharmacol. Exp. Ther.* (2001) 298:1172-1178; Pandey, A., *et al.*, *J. Med. Chem.* (2002) 45:3772-3793 Matsuno, K., *et al.*, *J. Med. Chem.* (2002) 45: 4413-4523 and Matsuno, K., *et al.*, *ibid.*, 3057-3066. Still another class is represented by 2-phenyl pyrimidines as disclosed by Buchdunger, E., *et al.*, *Proc. Natl. Acad. Sci. USA.* (1995) 92:2558-2562. However, there remains a need for additional compounds that are effective in inhibiting PDGFR kinase activity. Given the complexities of signal transduction with the redundancy and crosstalk between various pathways, the identification of specific PDGFR tyrosine kinase inhibitors permits accurate targeting with limited or no unwanted inhibition of the pathways, thus reducing the toxicity of such inhibitory compounds.

In one embodiment, compositions and methods provided herein are effective to modulate the activity of PDGFR. In other embodiments, compositions and methods provided herein are effective to selectively modulate the activity of PDGFR.

FLT-3

FLT3 kinase is a tyrosine kinase receptor involved in the regulation and stimulation of cellular proliferation. See *e.g.*, Gilliland *et al.*, *Blood* 100:1532-42 (2002). The FLT3 kinase is a member of the class III receptor tyrosine kinase (RTKIII) receptor family and belongs to the same subfamily of tyrosine kinases as c-kit, c-fms, and the platelet-derived growth factor

α and β receptors. See e.g., Lyman et al., *FLT3 Ligand in THE CYTOKINE HANDBOOK* 989 (Thomson et al., eds. 4th Ed.) (2003). The FLT3 kinase has five immunoglobulin-like domains in its extracellular region as well as an insert region of 75-100 amino acids in the middle of its cytoplasmic domain. FLT3 kinase is activated upon the binding of the FLT3 ligand, which causes receptor dimerization. Dimerization of the FLT3 kinase by FLT3 ligand activates the intracellular kinase activity as well as a cascade of downstream substrates including Stat5, Ras, phosphatidylinositol-3-kinase (PI3K), PLC γ , Erk2, Akt, MAPK, SHC, SHP2, and SHIP. See e.g., Rosnet et al., *Acta Haematol.* 95:218 (1996); Hayakawa et al., *Oncogene* 19:624 (2000); Mizuki et al., *Blood* 96:3907 (2000); and Gilliland et al., *Curr. Opin. Hematol.* 9: 274-81 (2002). Both membrane-bound and soluble FLT3 ligand bind, dimerize, and subsequently activate the FLT3 kinase.

In normal cells, immature hematopoietic cells, typically CD34+ cells, placenta, gonads, and brain express FLT3 kinase. See, e.g., Rosnet, et al., *Blood* 82:1110-19 (1993); Small et al., *Proc. Natl. Acad. Sci. U.S.A.* 91:459-63 (1994); and Rosnet et al., *Leukemia* 10:238-48 (1996). However, efficient stimulation of proliferation via FLT3 kinase typically requires other hematopoietic growth factors or interleukins. FLT3 kinase also plays a critical role in immune function through its regulation of dendritic cell proliferation and differentiation. See e.g., McKenna et al., *Blood* 95:3489-97 (2000).

Numerous hematologic malignancies express FLT3 kinase, the most prominent of which is AML. See e.g., Yokota et al., *Leukemia* 11:1605-09 (1997). Other FLT3 expressing malignancies include B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias. See e.g., Rasko et al., *Leukemia* 9:2058-66 (1995).

FLT3 kinase mutations associated with hematologic malignancies are activating mutations. In other words, the FLT3 kinase is constitutively activated without the need for binding and dimerization by FLT3 ligand, and therefore stimulates the cell to grow continuously.

Several studies have identified inhibitors of FLT3 kinase activity that also inhibit the kinase activity of related receptors, e.g., VEGF receptor (VEGFR), PDGF receptor (PDGFR), and kit receptor kinases. See e.g., Mendel et al., *Clin. Cancer Res.* 9:327-37 (2003); O'Farrell et al., *Blood* 101:3597-605 (2003); and Sun et al., *J. Med. Chem.* 46:1116-

19 (2003). Such compounds effectively inhibit FLT3 kinase-mediated phosphorylation, cytokine production, cellular proliferation, resulting in the induction of apoptosis. *See e.g.*, Spiekermann et al., *Blood* 101:1494-1504 (2003). Moreover, such compounds have potent antitumor activity *in vitro* and *in vivo*.

5 In some embodiments, the kinase is a class III receptor tyrosine kinase (RTKIII). In other embodiments, the kinase is a tyrosine kinase receptor intimately involved in the regulation and stimulation of cellular proliferation. In still other embodiments, the kinase is a fms-like tyrosine kinase 3 receptor (FLT-3 kinase). In this context, inhibition and reduction of the activity of FLT-3 kinase refers to a lower level of measured activity relative to a
10 control experiment in which the protein, cell, or subject is not treated with the test compound, whereas an increase in the activity of FLT-3 kinase refers to a higher level of measured activity relative to a control experiment. In particular embodiments, the reduction or increase is at least 10%. One of skill in the art will appreciate that reduction or increase in the activity of FLT-3 kinase of at least 20%, 50%, 75%, 90% or 100% or any integer between 10% and
15 100% may be preferred for particular applications.

Compounds provided herein are useful in treating conditions characterized by inappropriate FLT3 activity such as proliferative disorders. FLT3 activity includes, but is not limited to, enhanced FLT3 activity resulting from increased or *de novo* expression of FLT3 in cells, increased FLT3 expression or activity, and FLT3 mutations resulting in constitutive
20 activation. The existence of inappropriate or abnormal FLT3 ligand and FLT3 levels or activity can be determined using well known methods in the art. For example, abnormally high FLT3 levels can be determined using commercially available ELISA kits. FLT3 levels can be determined using flow cytometric analysis, immunohistochemical analysis, and *in situ* hybridization techniques.

25 An inappropriate activation of the FLT3 can be determined by an increase in one or more of the activities occurring subsequent to FLT3 binding: (1) phosphorylation or autophosphorylation of FLT3; (2) phosphorylation of a FLT3 substrate, *e.g.*, Stat5, Ras; (3) activation of a related complex, *e.g.*, PI3K; (4) activation of an adaptor molecule; and (5) cellular proliferation. These activities are readily measured by well known methods in the art.

30 *Formulations*

The compounds described herein can be used to prepare a medicament, such as by

formulation into pharmaceutical compositions for administration to a subject using techniques generally known in the art. A summary of such pharmaceutical compositions may be found, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA. The compounds of the invention can be used singly or as components of mixtures. Preferred forms of the compounds are those for systemic administration as well as those for topical or transdermal administration. Formulations designed for timed release are also within the scope of the invention. Formulation in unit dosage form is also preferred for the practice of the invention.

In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compounds. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packeted tablets or capsules, and powders in vials or ampoules.

The compounds described herein may be labeled isotopically (e.g. with a radioisotope) or by any other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels. The compositions may be in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. Suitable excipients or carriers are, for example, water, saline, dextrose, glycerol, alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like. Of course, these compositions may also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

Methods for the preparation of compositions comprising the compounds described herein include formulating the derivatives with one or more inert, pharmaceutically acceptable carriers to form either a solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein.

A carrier of the invention can be one or more substances which also serve to act as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, or tablet disintegrating agent. A carrier can also be an encapsulating material.

In powder forms of the compositions, the carrier is preferably a finely divided solid in powder form which is interdispersed as a mixture with a finely divided powder from of one or more compound. In tablet forms of the compositions, one or more compounds is intermixed with a carrier with appropriate binding properties in suitable proportions followed by compaction into the shape and size desired. Powder and tablet form compositions preferably contain between about 5 to about 70% by weight of one or more compound. Carriers that may be used in the practice of the invention include, but are not limited to, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The compounds of the invention may also be encapsulated or microencapsulated by an encapsulating material, which may thus serve as a carrier, to provide a capsule in which the derivatives, with or without other carriers, is surrounded by the encapsulating material. In an analogous manner, cachets comprising one or more compounds are also provided by the instant invention. Tablet, powder, capsule, and cachet forms of the invention can be formulated as single or unit dosage forms suitable for administration, optionally conducted orally.

In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted. One or more compounds are then dispersed into the melted material by, as a non-limiting example, stirring. The non-solid mixture is then placed into molds as desired and allowed to cool and solidify.

Non-limiting compositions in liquid form include solutions suitable for oral or parenteral administration, as well as suspensions and emulsions suitable for oral administration. Sterile aqueous based solutions of one or more compounds, optionally in the presence of an agent to increase solubility of the derivative(s), are also provided. Non-limiting examples of sterile solutions include those comprising water, ethanol, and/or propylene glycol in forms suitable for parenteral administration. A sterile solution of the invention may be prepared by dissolving one or more compounds in a desired solvent followed by sterilization, such as by filtration through a sterilizing membrane filter as a non-limiting example. In another embodiment, one or more compounds are dissolved into a previously sterilized solvent under

sterile conditions.

A water based solution suitable for oral administration can be prepared by dissolving one or more compounds in water and adding suitable flavoring agents, coloring agents, stabilizers, and thickening agents as desired. Water based suspensions for oral use can be made by dispersing one or more compounds in water together with a viscous material such as, but not limited to, natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, and other suspending agents known to the pharmaceutical field.

In therapeutic use, the compounds of the invention are administered to a subject at dosage levels of from about 0.5 mg/kg to about 8.0 mg/kg of body weight per day. For example, a human subject of approximately 70 kg, this is a dosage of from 35 mg to 560 mg per day. Such dosages, however, may be altered depending on a number of variables, not limited to the activity of the compound used, the condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the condition being treated, and the judgment of the practitioner.

The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon.

Methods of Use

By modulating kinase activity, the compounds disclosed herein can be used to treat a variety of diseases. Suitable conditions characterized by undesirable protein-kinase activity can be treated by the compounds presented herein. As used herein, the term "condition" refers to a disease, disorder, or related symptom where inappropriate kinase activity is present. In some embodiments, these conditions are characterized by aggressive neovascularization including tumors, especially acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs). In some embodiments, a FLT3 modulating compounds may be used to treat tumors. The ability of compounds that inhibit FLT3 kinase activity to treat tumors has been established.

Compounds having this property include SU5416 (Sugen), PKC412 (Novartis), GTP-14564 and CT53518 (Millennium). See e.g., Giles et al., *Blood* 102:795-801 (2003); Weisberg et

al., *Cancer Cell* 1:433-43 (2002); Murata et al., *J. Biol. Chem.* 278:32892-98 (2003); and Kelly et al., *Cancer Cell* 1:421-32 (2002).

Compounds presented herein are useful in the treatment of a variety of biologically aberrant conditions or disorders related to tyrosine kinase signal transduction. Such disorders pertain to abnormal cell proliferation, differentiation, and/or metabolism. Abnormal cell proliferation may result in a wide array of diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis).

In various embodiments, compounds presented herein regulate, modulate, and/or inhibit disorders associated with abnormal cell proliferation by affecting the enzymatic activity of one or more tyrosine kinases and interfering with the signal transduced by said kinase. More particularly, the present invention is directed to compounds which regulate, modulate said kinase mediated signal transduction pathways as a therapeutic approach to cure leukemia and many kinds of solid tumors, including but not limited to carcinoma, sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreas cancers, colon cancers, blood cancers, lung cancers and bone cancers.

In other embodiments, compounds herein are useful in the treatment of cell proliferative disorders including cancers, blood vessel proliferative disorders, fibrotic disorders, and mesangial cell proliferative disorders. Blood vessel proliferation disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration. They also play a pivotal role in cancer development. Other examples of blood vessel proliferation disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage, and ocular diseases, like diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness. Conversely, disorders related to the shrinkage, contraction or closing of blood vessels, such as restenosis, are also implicated.

Fibrotic disorders refer to the abnormal formation of extracellular matrix. Examples of fibrotic disorders include hepatic cirrhosis and mesangial cell proliferative disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar. Hepatic cirrhosis can cause diseases such as cirrhosis of the liver. An increased extracellular matrix resulting in a hepatic scar can also be caused by viral infection such as hepatitis. Lipocytes appear to play a major role in hepatic cirrhosis. Other fibrotic disorders implicated include atherosclerosis (see, below).

Mesangial cell proliferative disorders refer to disorders brought about by abnormal proliferation of mesangial cells. Mesangial proliferative disorders include various human renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies. The cell proliferative disorders which are indications of the present invention are not necessarily independent. For example, fibrotic disorders may be related to, or overlap, with blood vessel proliferative disorders. For example, atherosclerosis results, in part, in the abnormal formation of fibrous tissue within blood vessels.

Compounds of the invention can be administered to a subject upon determination of the subject as having a disease or unwanted condition that would benefit by treatment with said derivative. The determination can be made by medical or clinical personnel as part of a diagnosis of a disease or condition in a subject. Non-limiting examples include determination of a risk of acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs).

The methods of the invention can comprise the administration of an effective amount of one or more compounds as disclosed herein, optionally in combination with one or more other active agents for the treatment of a disease or unwanted condition as disclosed herein. The subject is preferably human, and repeated administration over time is within the scope of the present invention.

The present invention thus also provides compounds described above and their salts or solvates and pharmaceutically acceptable salts or solvates thereof for use in the prevention or treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds of the present

invention are especially useful for the treatment of disorders caused by aberrant kinase activity such as breast, ovarian, gastric, pancreatic, non-small cell lung, bladder, head and neck cancers, and psoriasis. The cancers include hematologic cancers, for example, acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs).

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity, including susceptible malignancies, which comprises administering to the subject an effective amount of a compound described above or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the present invention provides the use of a compound described above, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of cancer and malignant tumors. The cancer can be stomach, gastric, bone, ovary, colon, lung, brain, larynx, lymphatic system, genitourinary tract, ovarian, squamous cell carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, lung cancer, bladder cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, breast cancer, small-cell lung cancer, leukemia, acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs), glioma, colorectal cancer, genitourinary cancer gastrointestinal cancer, or pancreatic cancer.

In accordance with the present invention, compounds provided herein are useful for preventing and treating conditions associated with ischemic cell death, such as myocardial infarction, stroke, glaucoma, and other neurodegenerative conditions. Various neurodegenerative conditions which may involve apoptotic cell death, include, but are not limited to, Alzheimer's Disease, ALS and motor neuron degeneration, Parkinson's disease, peripheral neuropathies, Down's Syndrome, age related macular degeneration (ARMD), traumatic brain injury, spinal cord injury, Huntington's Disease, spinal muscular atrophy, and HIV encephalitis. The compounds described in detail above can be used in methods and compositions for imparting neuroprotection and for treating neurodegenerative diseases.

The compounds described herein, can be used in a pharmaceutical composition for the

prevention and/or the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis and rheumatoid arthritis), common cold, dysmenorrhea, menstrual cramps, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familial adenomatous polyposis), tissue ulceration, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding, coagulation, anemia, synovitis, gout, ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neurodegenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic retinopathy, neuropathy and nephropathy), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders, and septic shock, arthritis, fever, common cold, pain and cancer in a mammal, preferably a human, cat, livestock or a dog, comprising an amount of a compound described herein or a pharmaceutically acceptable salt thereof effective in such

prevention and/or treatment optionally with a pharmaceutically acceptable carrier.

A further aspect of the present invention provides the use of a compound described above, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of psoriasis.

5 As one of skill in the art will recognize, the compounds can be administered before, during or after the occurrence of a condition or a disease, and the timing of administering the composition containing a compound can vary. Thus, for example, the compounds can be used as a prophylactic and can be administered continuously to subjects with a propensity to conditions and diseases in order to prevent the occurrence of the disorder. The compounds
10 and compositions can be administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the compounds can be initiated within the first 48 hours of the onset of the symptoms, preferably within the first 48 hours of the onset of the symptoms, more preferably within the first 6 hours of the onset of the symptoms, and most preferably within 3 hours of the onset of the symptoms. The initial administration can be via
15 any route practical, such as, for example, an intravenous injection, a bolus injection, infusion over 5 min. to about 5 hours, a pill, a capsule, transdermal patch, buccal delivery, and the like, or a combination thereof. A compound is preferably administered as soon as is practicable after the onset of a condition or a disease is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1
20 month to about 3 months. As one of skill in the art will recognize, the length of treatment can vary for each subject, and the length can be determined using the known criteria. For example, the compound or a formulation containing the compound can be administered for at least 2 weeks, preferably about 1 month to about 5 years, and more preferably from about 1 month to about 3 years.

25 *Kits/Articles of Manufacture*

For use in the therapeutic applications described herein, kits and articles of manufacture are also within the scope of the invention. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a
30 method of the invention. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or

plastic.

For example, the container(s) can comprise one or more compounds of the invention, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods of the present invention.

A kit of the invention will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound of the invention. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

The terms "kit" and "article of manufacture" may be used as synonyms.

EXAMPLES

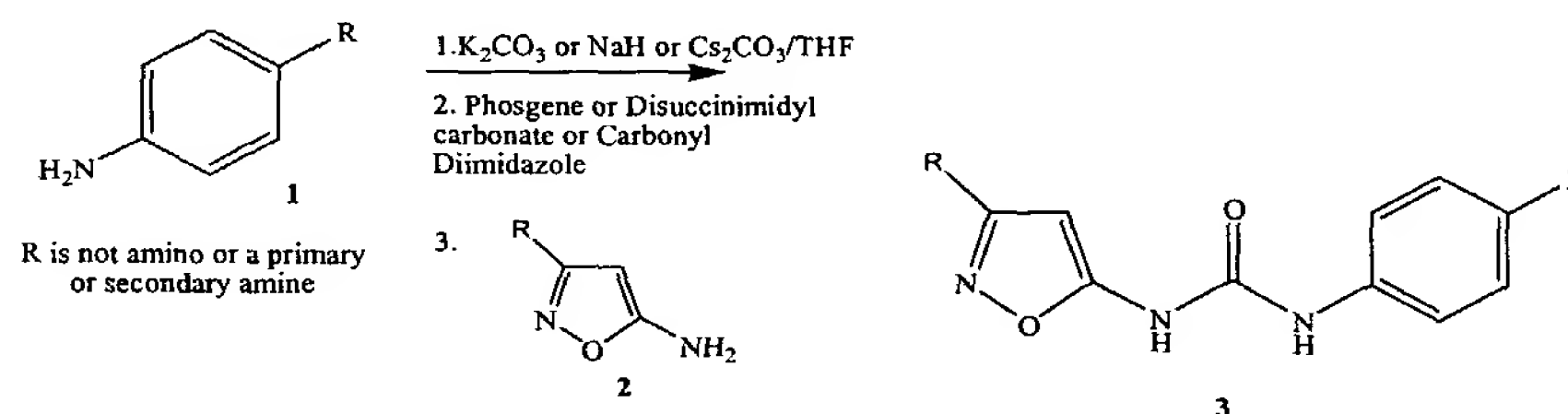
The present invention is further illustrated by the following examples, which should not be construed as limiting in any way. The experimental procedures to generate the data shown are discussed in more detail below. For all formulations herein, multiple doses may be proportionally compounded as is known in the art. The coatings, layers and encapsulations are applied in conventional ways using equipment customary for these purposes.

The invention has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation. Thus, it will be appreciated by those of skill in the art that conditions such as choice of

solvent, temperature of reaction, volumes, reaction time may vary while still producing the desired compounds. In addition, one of skill in the art will also appreciate that many of the reagents provided in the following examples may be substituted with other suitable reagents. See, e.g., Smith & March, Advanced Organic Chemistry, 5th ed. (2001).

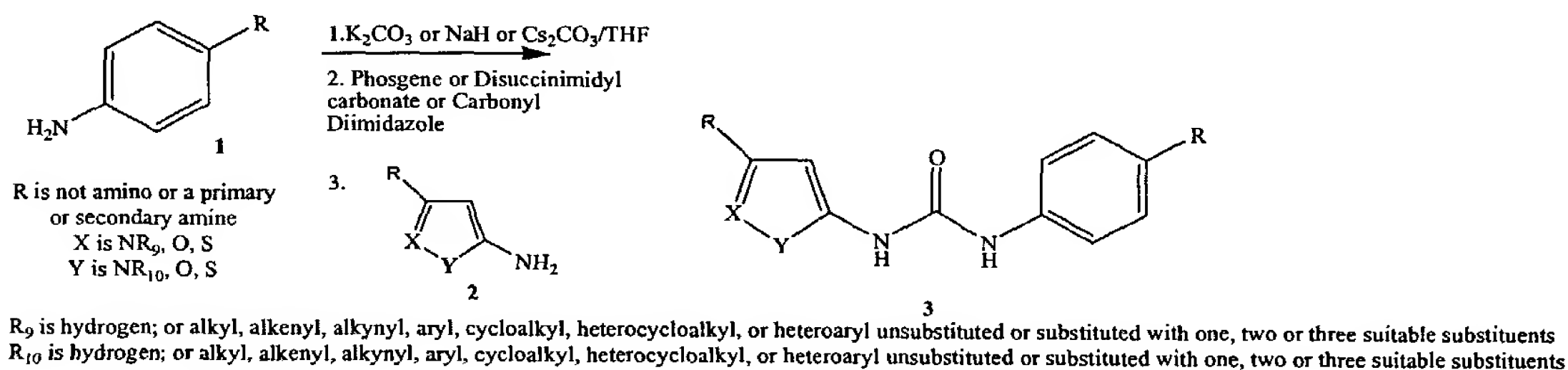
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Example A: Synthesis of Isoxazole-Ureas



A mixture of amine 1 (1 eq) in dry THF is stirred at room temperature under argon for an hour. Then the stirred suspension is cooled to 0°C and to it is added dropwise a solution of phosgene or disuccinimidyl carbonate or carbonyl diimidazole (1.2 eq). The reaction is stirred at 0°C for half an hour. An isoxazol-amine 2 in THF is added dropwise and the reaction is allowed to warm to room temperature and stirred overnight. The solvent is removed and extracted with ethyl acetate and water. The organic layer is dried over magnesium sulfate and solvent removed, and the product 3 purified by HPLC.

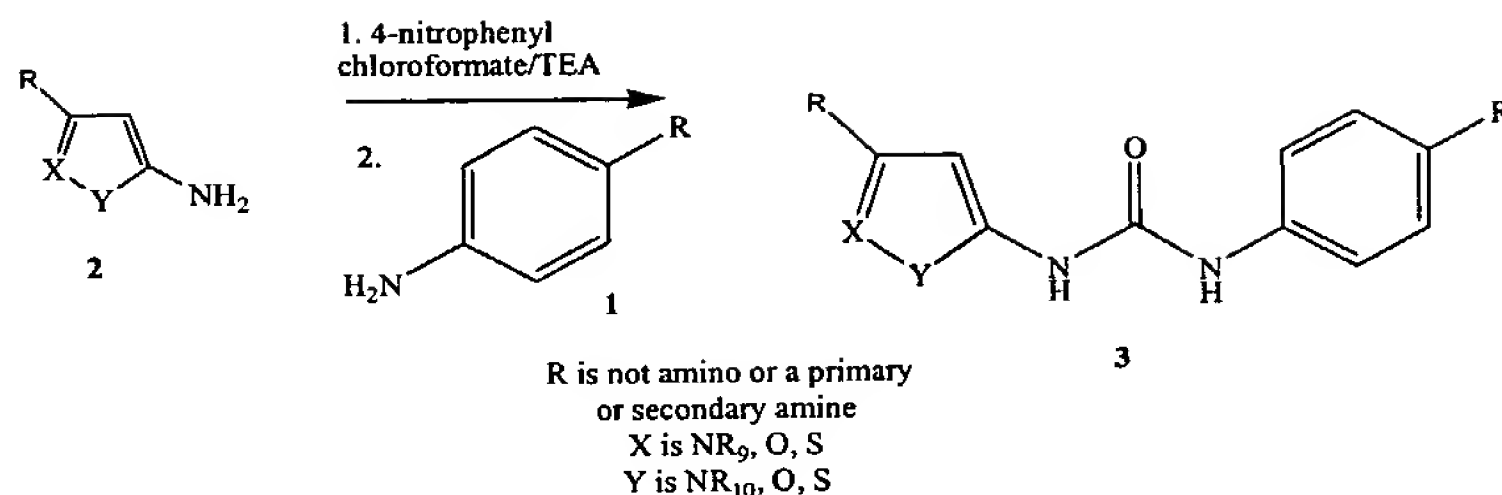
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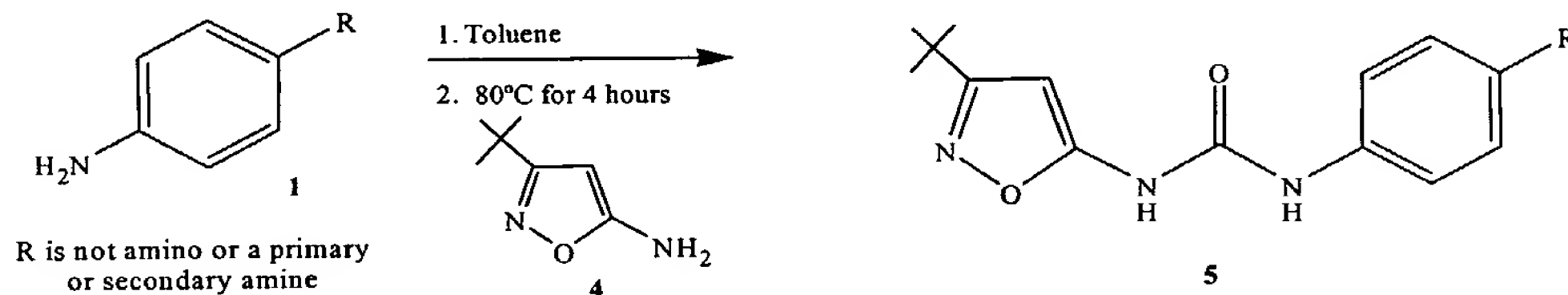
Alternatively, to a stirring solution of an isoxazol-amine 2 (1eq) in THF, a mixture of 4-nitrophenyl chloroformate (1.2 eq) and triethyl amine (1.2 eq) is added dropwise at 0°C. The reaction is stirred for two hours at room temperature and the aniline 1 is added. The reaction is refluxed to 80°C for six hours. The mixture is cooled to room temperature and poured into water and extracted with ethyl acetate and dried over magnesium sulfate, and the product 3 purified by HPLC.

20

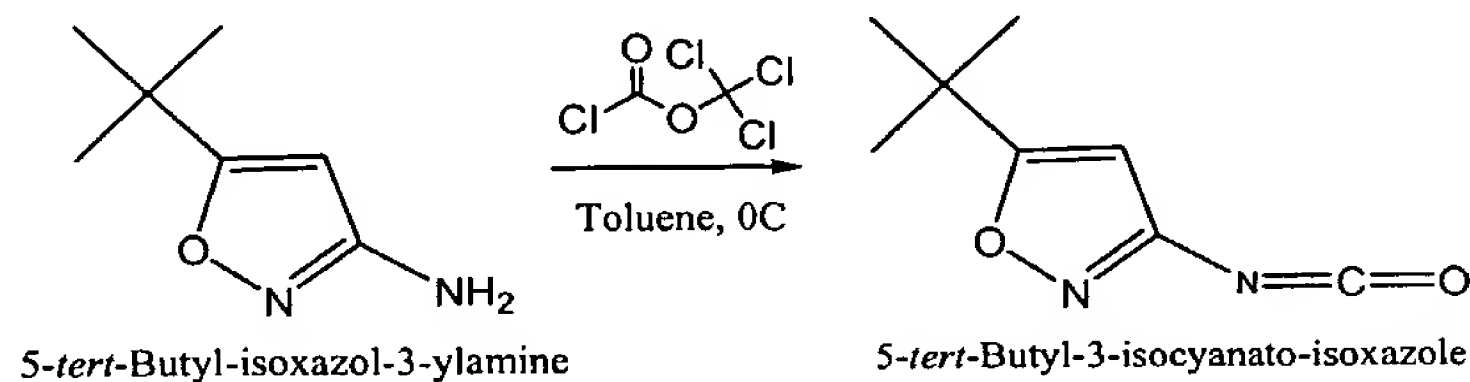
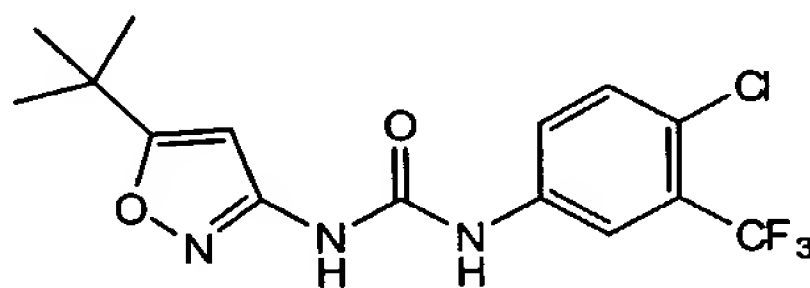


R₉ is hydrogen; or alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl unsubstituted or substituted with one, two or three suitable substituents
R₁₀ is hydrogen; or alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl unsubstituted or substituted with one, two or three suitable substituents

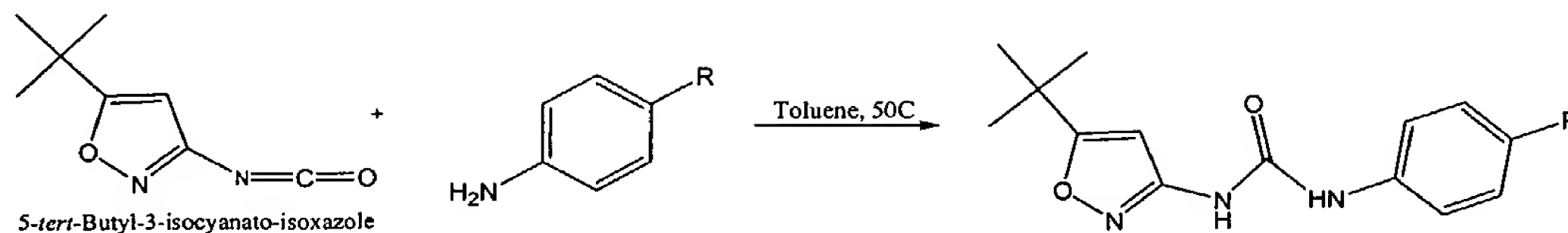
Alternatively, amine 1 (1 eq) is dissolved in toluene at room temperature and stirred for 10 minutes. Then 3-tert-butyl-isoxazol-5-yl isocyanate 4 in toluene is added and heated at 80°C for 4 hours. The solvent is removed and the crude mixture is purified by HPLC to obtain 5.



Synthesis of Compound A1: 1-(5-tert-butylisoxazol-3-yl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea



To a stirring solution of 5-tert-Butyl-isoxazol-3-ylamine (250mg, 1eq) in dry toluene at 0°C trichloromethyl chloroformate (1.1eq) was added dropwise. The reaction stirred at 0°C and allowed to warm to room temperature overnight. The solvent was removed and the mixture was recrystallized in ethyl acetate. The solid was filtered off and washed with cold ethyl acetate. Yield: 242mg (83%).

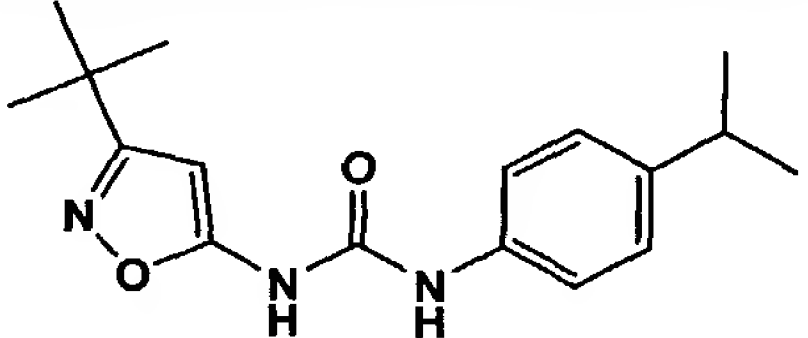
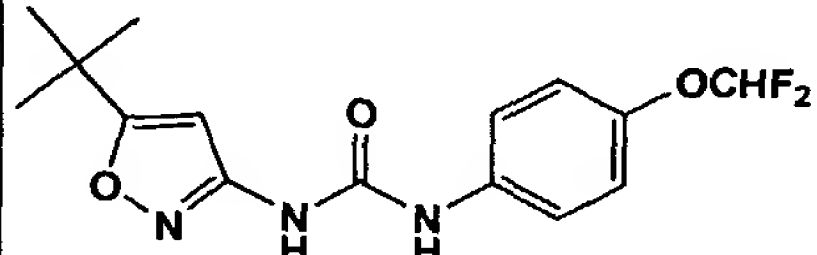
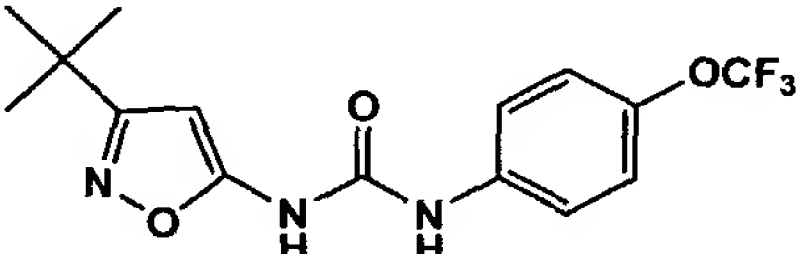
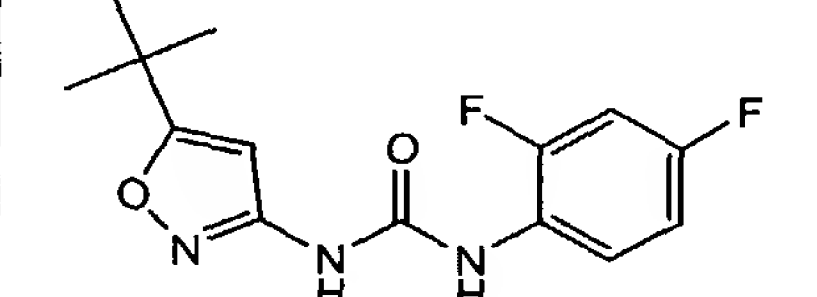
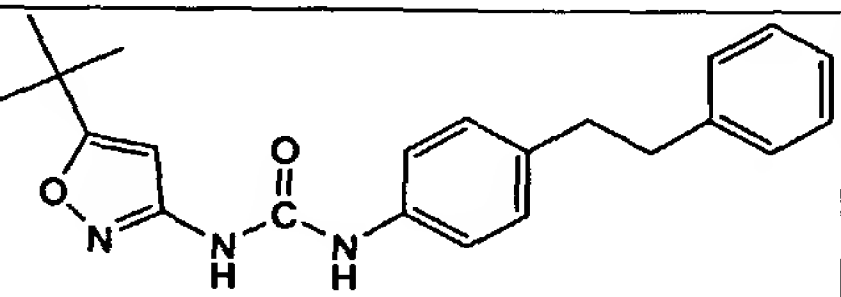
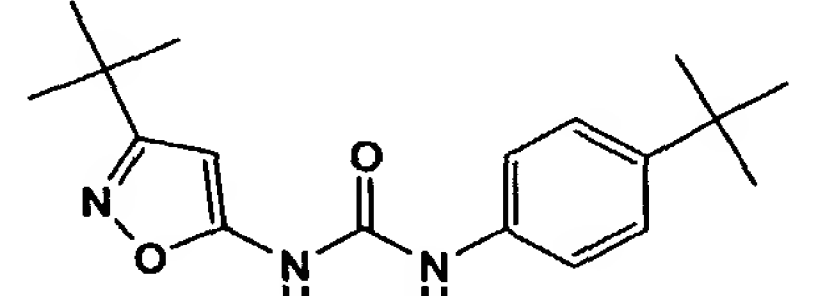
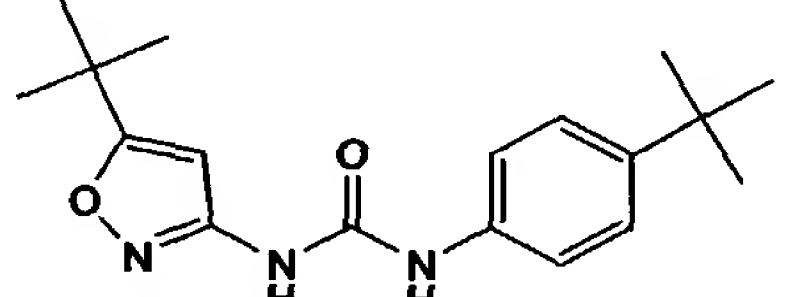
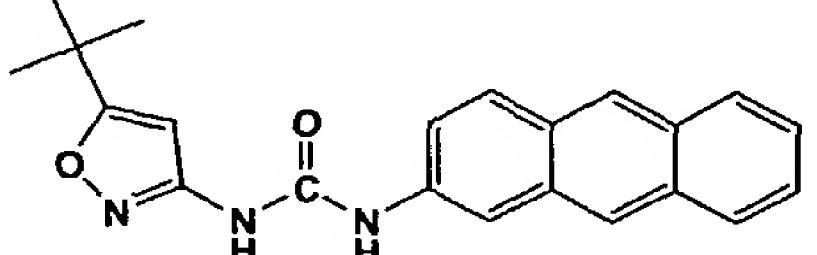
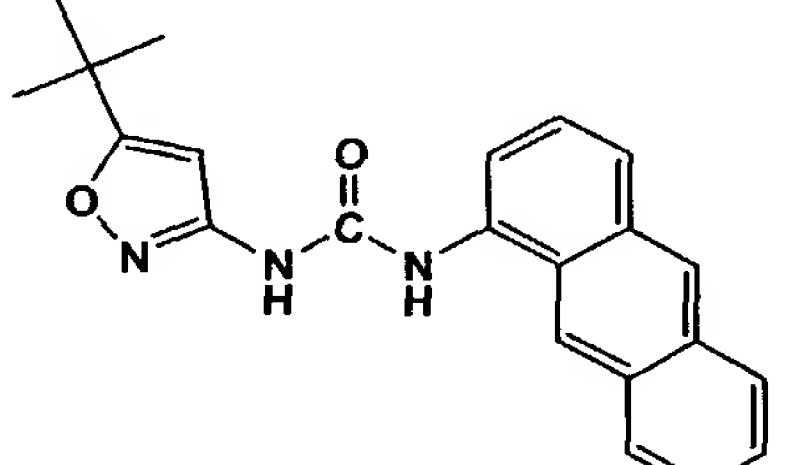
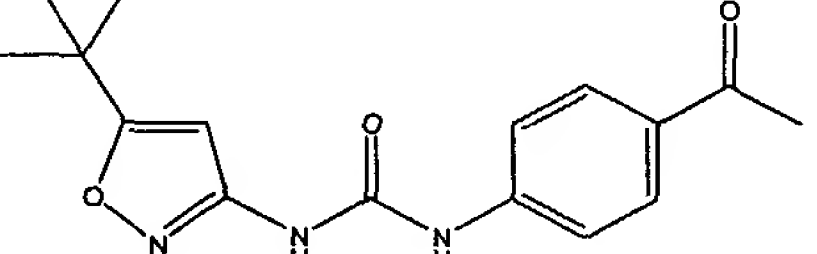
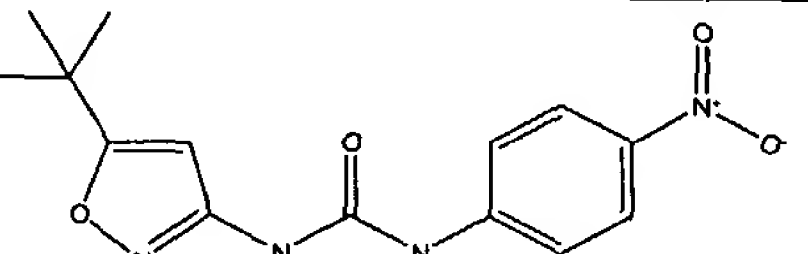
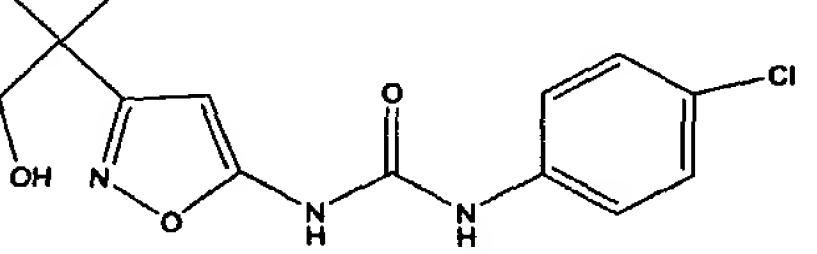
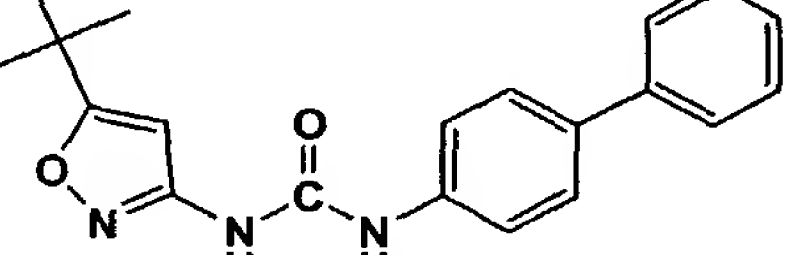
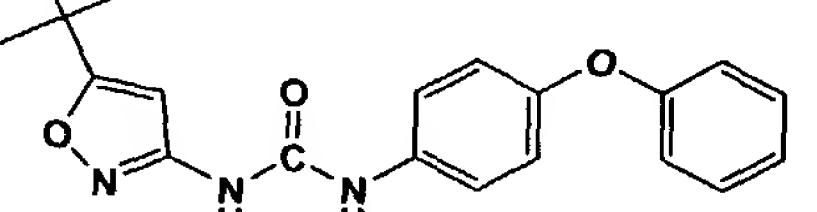
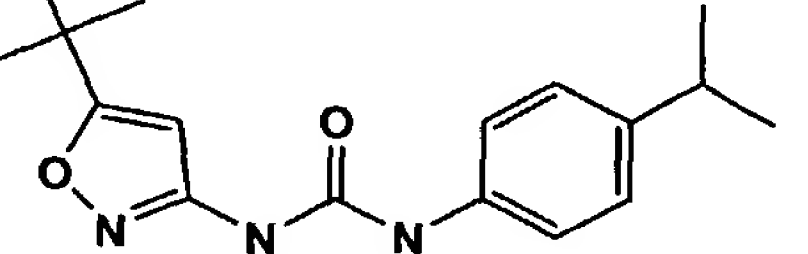
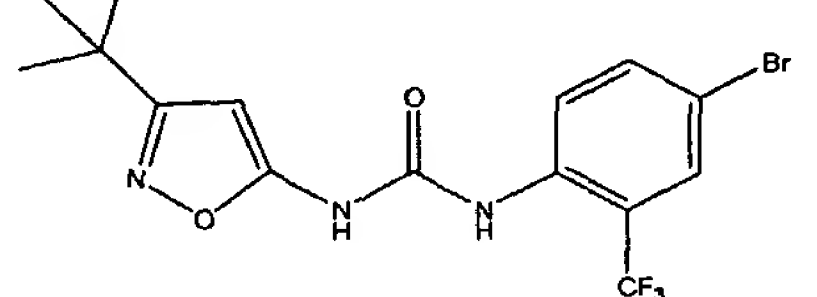


To a flask 5-tert-Butyl-3-isocyanato-isoxazole (242mg, 1eq) and substituted aniline (159mg, 1eq) was added and dissolved in toluene. The reaction was allowed to stir at 50°C for three hours. The solvent was removed and the mixture was purified by HPLC. Yield: 188mg (47%).

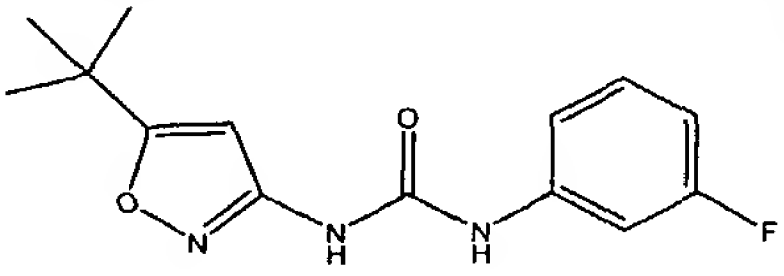
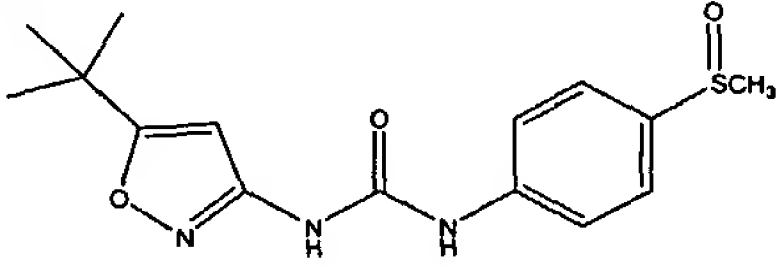
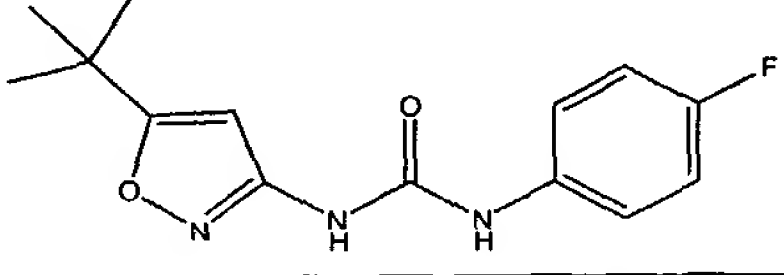
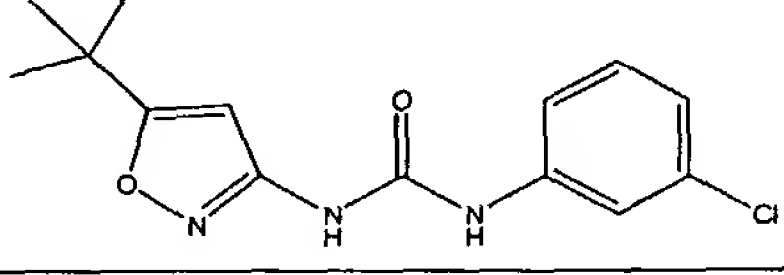
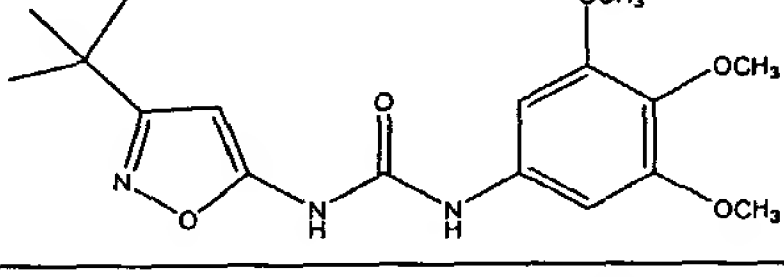
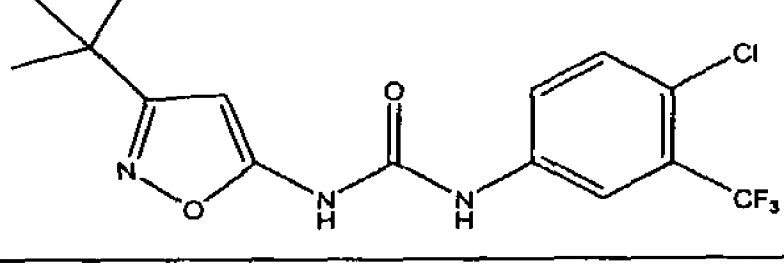
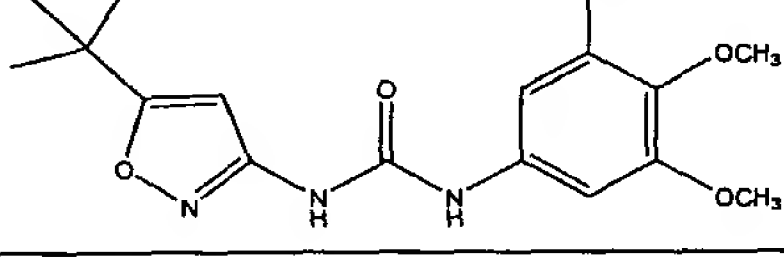
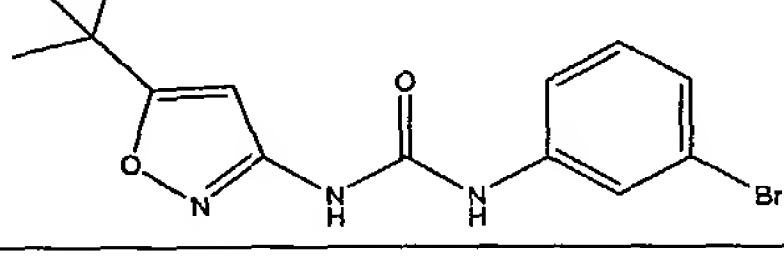
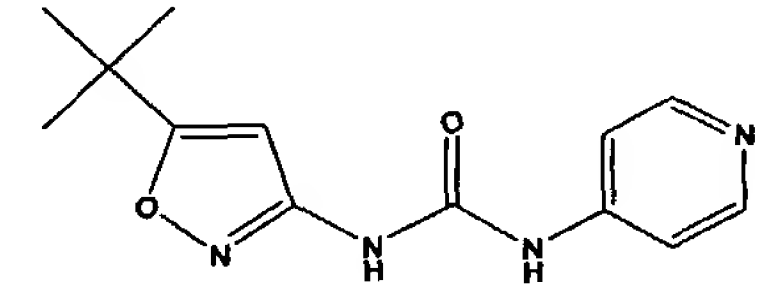
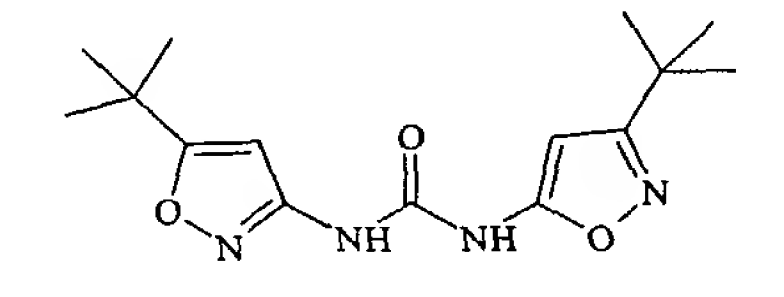
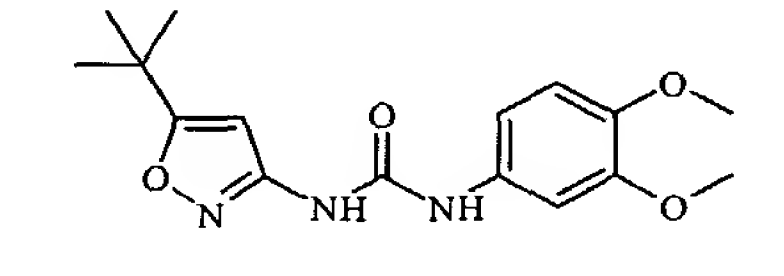
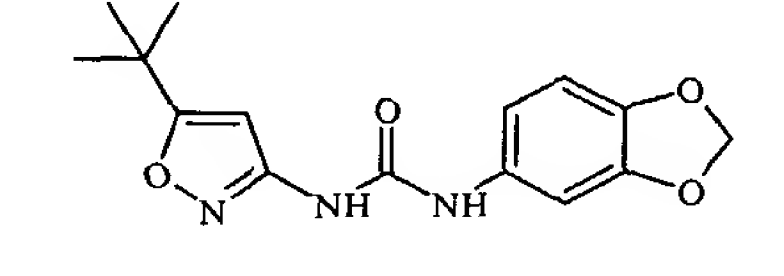
Compounds A2 through A57 were synthesized in a manner analogous to Compound A1 using similar starting materials and reagents. The structures are shown below in Table A:

Table A

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
A1		A2	
A3		A4	
A5		A6	
A7		A8	
A9		A10	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
A11		A12	
A13		A14	
A15		A16	
A17		A18	
A19		A20	
A21		A22	
A23		A24	
A25		A26	

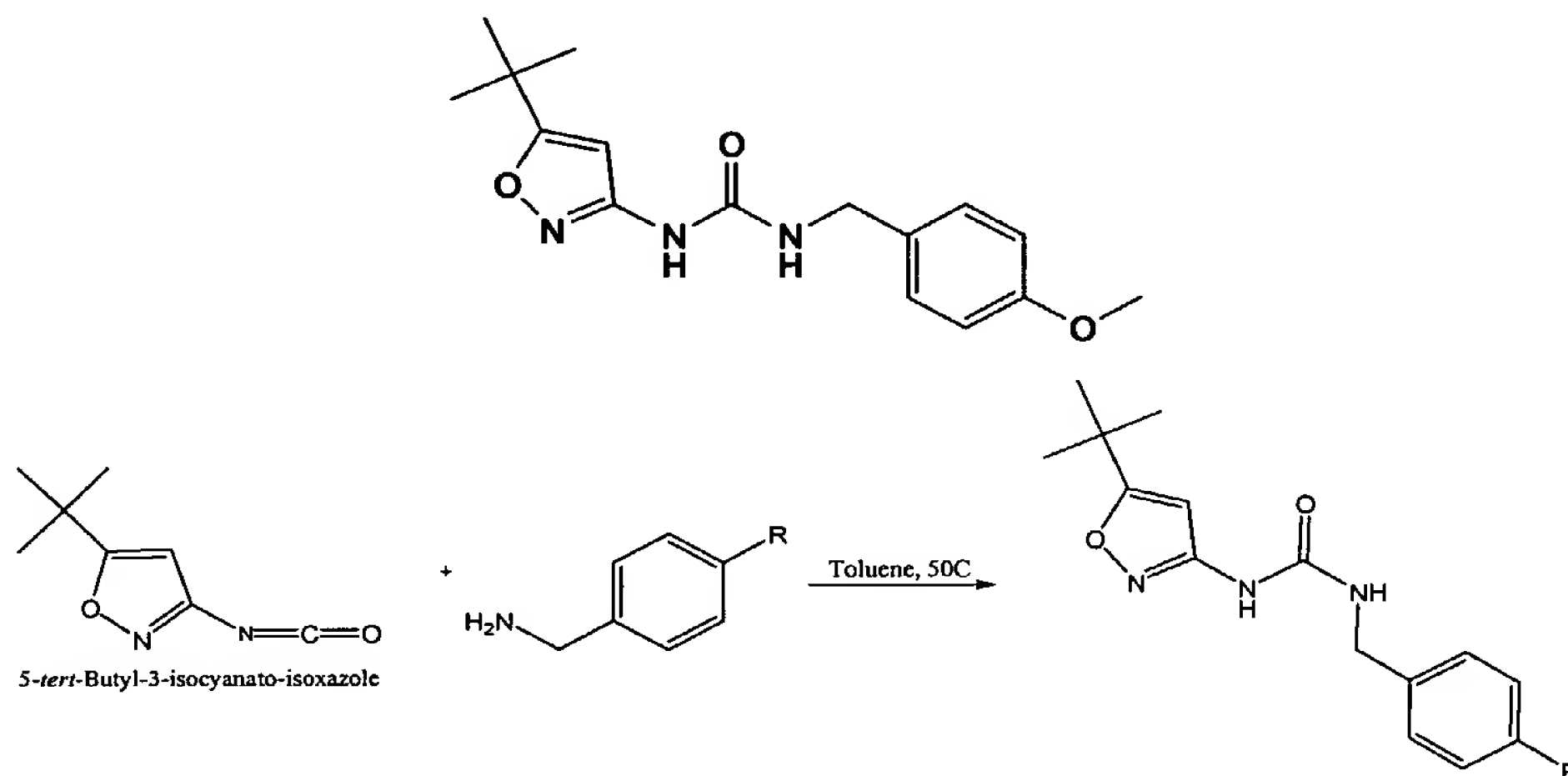
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
A27		A28	
A29		A30	
A31		A32	
A33		A34	
A35		A36	
A37		A38	
A39		A40	
A41		A42	
A43		A44	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
A45		A46	
A47		A48	
A49		A50	
A51		A52	
A53		A54	
A55		A56	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
A57			

Example B: Synthesis of alkyl-ureas

Synthesis of Compound B1: 1-(4-methoxybenzyl)-3-(5-tert-butylisoxazol-3-yl)urea



5

To a flask 5-tert-Butyl-3-isocyanato-isoxazole (242mg, 1eq) and substituted benzylamine (1eq) was added and dissolved in toluene. The reaction was allowed to stir at 50°C for three hours. The solvent removed and the mixture was purified by HPLC. Yield: 188mg (47%).

Compounds B2 through B8 were synthesized in a manner analogous to Compound B1 using similar starting materials and reagents. The structures are shown below in Table B:

10

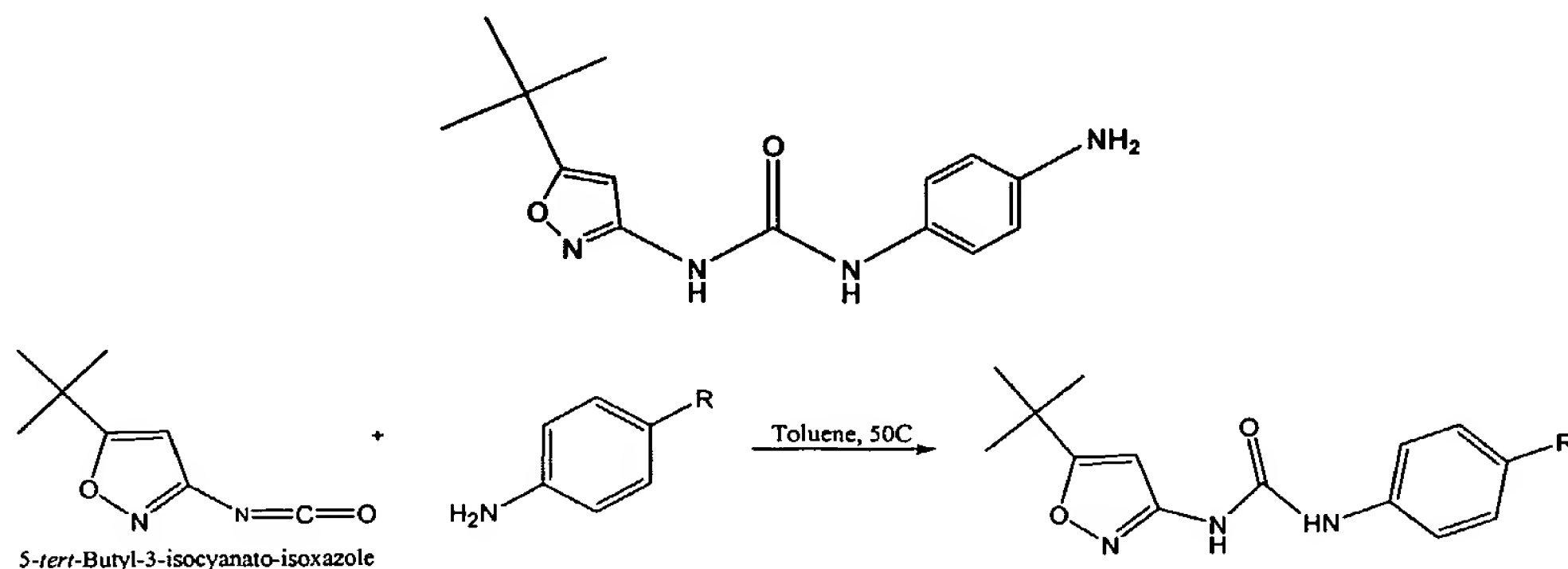
Table B

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
B1		B2	
B3		B4	
B5		B6	
B7		B8	

Example C: Synthesis of Reactive Ureas

Synthesis of Compound C1: 1-(5-tert-butylisoxazol-3-yl)-3-(4-aminophenyl)urea



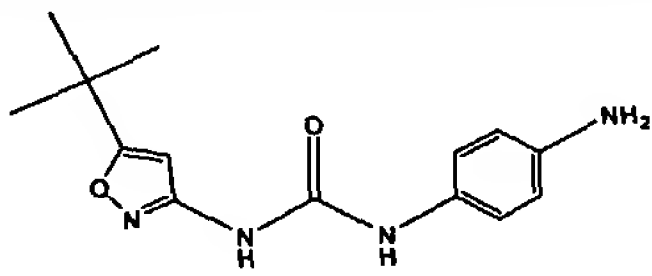
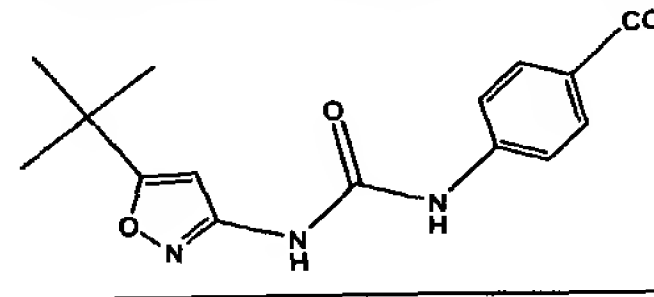
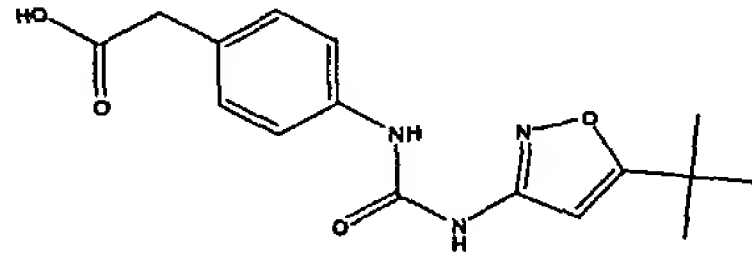
5

To a flask 5-tert-Butyl-3-isocyanato-isoxazole (242mg, 1eq) and substituted aniline

(159mg, 1eq) was added and dissolved in toluene. The reaction was allowed to stir at 50°C for three hours. The solvent removed and the mixture was purified by HPLC. Yield: 188mg (47%).

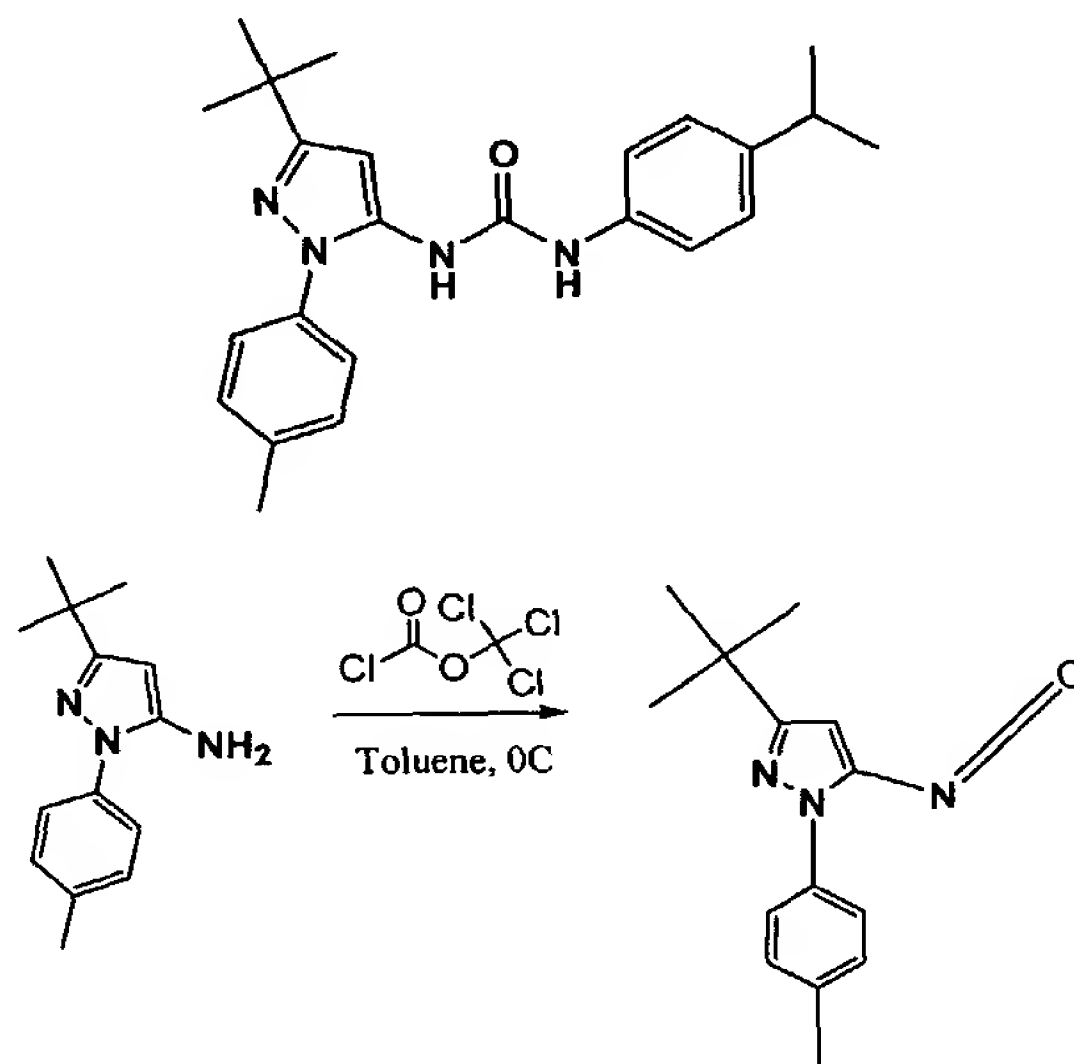
Compounds C2 through C3 were synthesized in a manner analogous to Compound C1 using similar starting materials and reagents. The structures are shown below in Table C:

Table C

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
C1		C2	
C3			

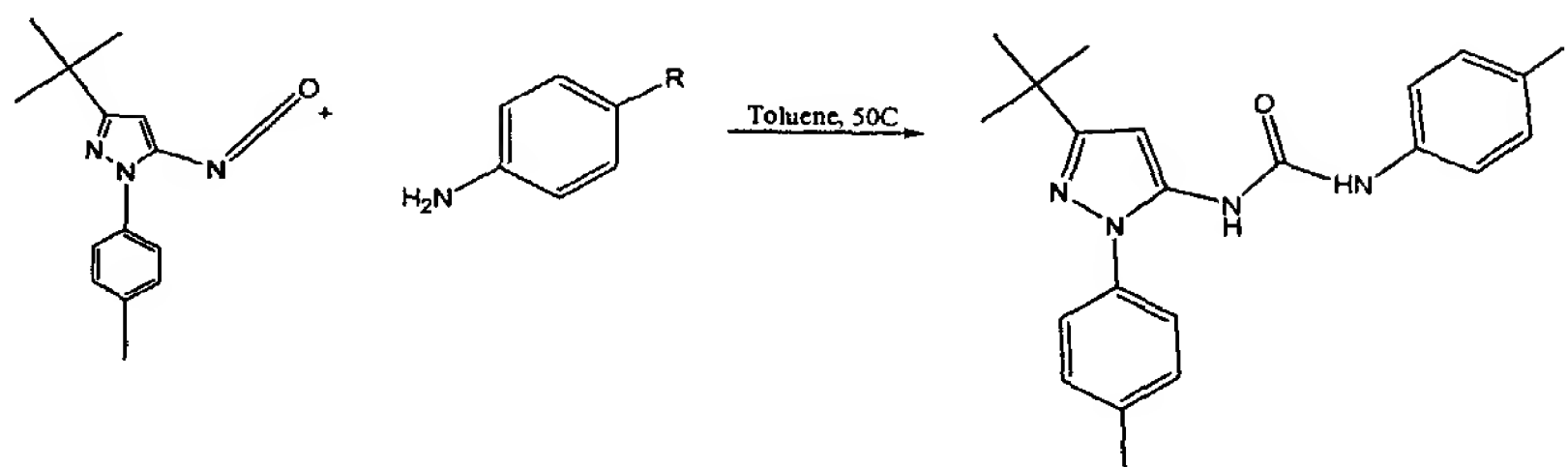
Example D: Synthesis of Substituted-Pyrazole Ureas

Synthesis of Compound D1: 1-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(4-isopropylphenyl)urea



To a stirring solution of 5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-ylamine (250mg, 1eq) in dry toluene at 0°C trichloromethyl chloroformate (1.1eq) was added dropwise. The reaction stirred at 0°C and allowed to warm to room temperature overnight. The solvent was removed and the mixture was recrystallized in ethyl acetate. The solid was filtered off and

washed with cold ethyl acetate. Yield: 242mg (83%).

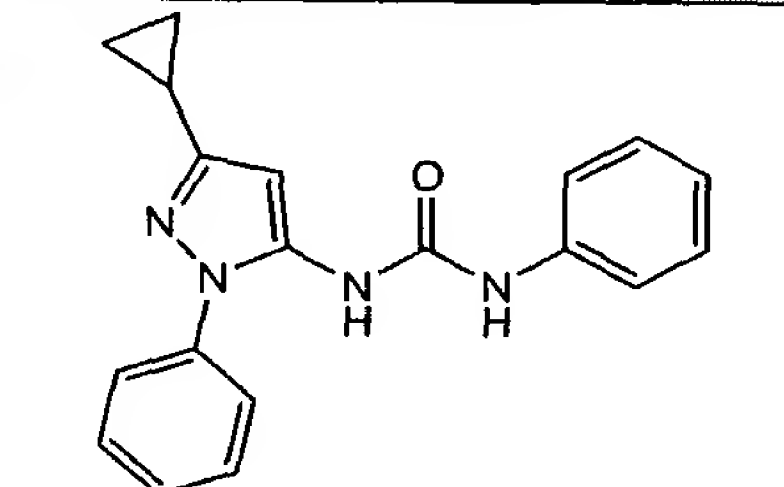
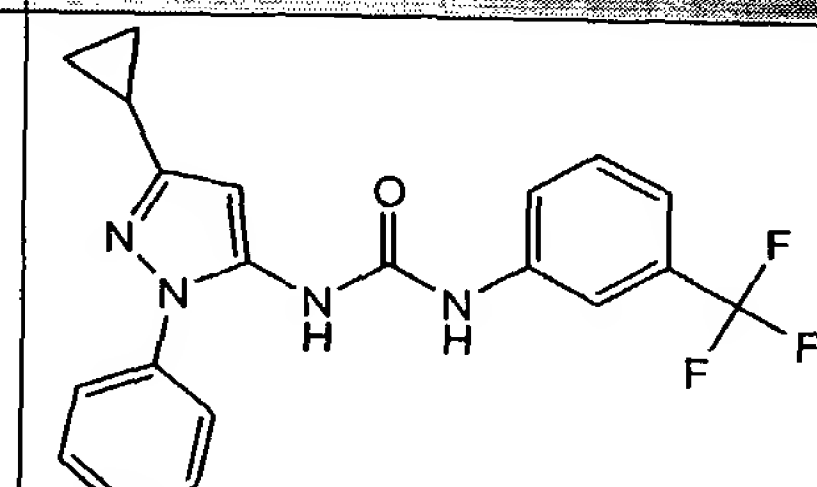
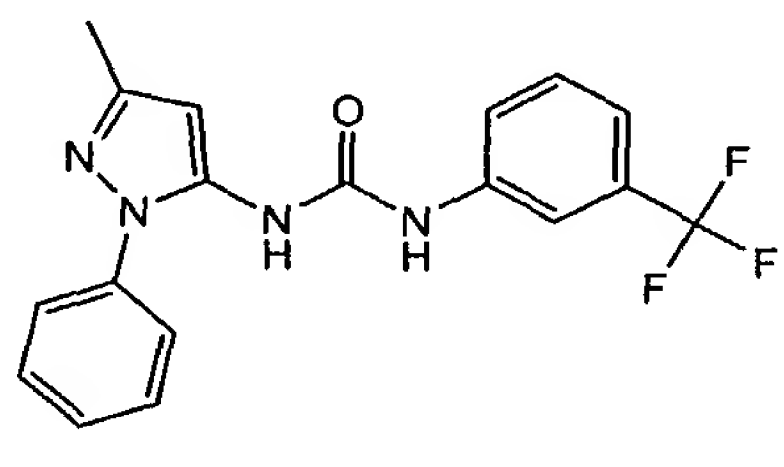
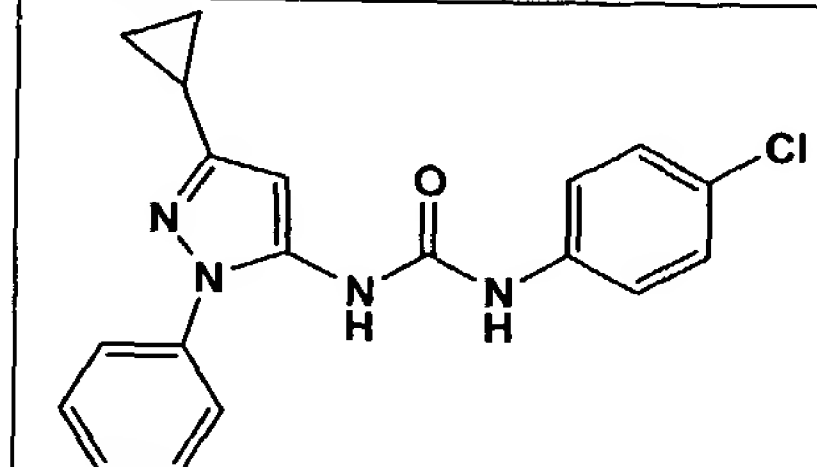
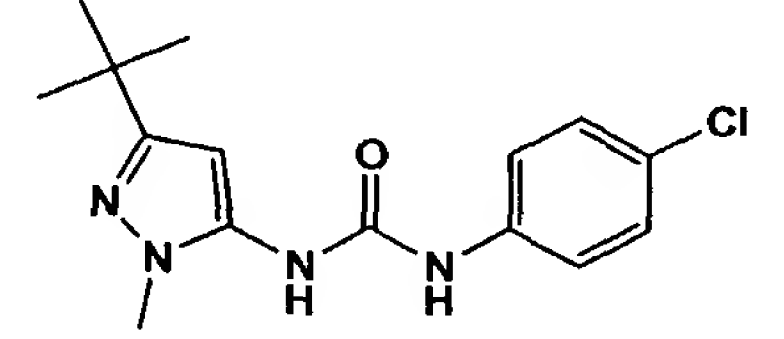
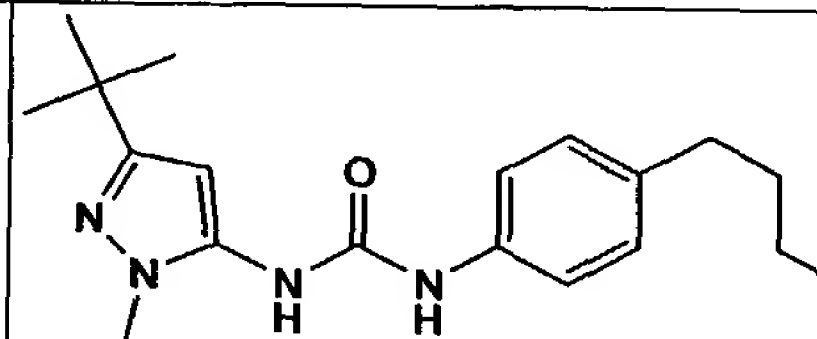
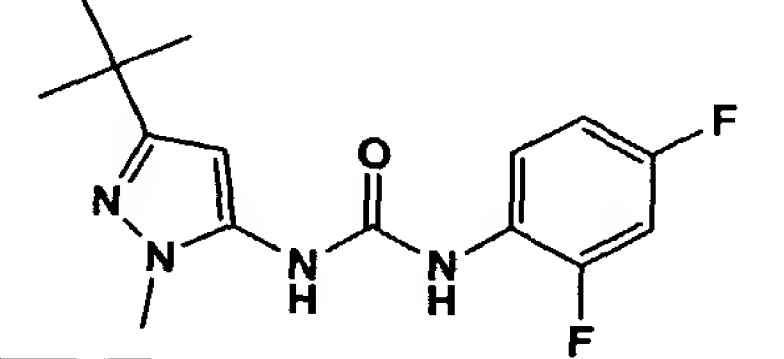
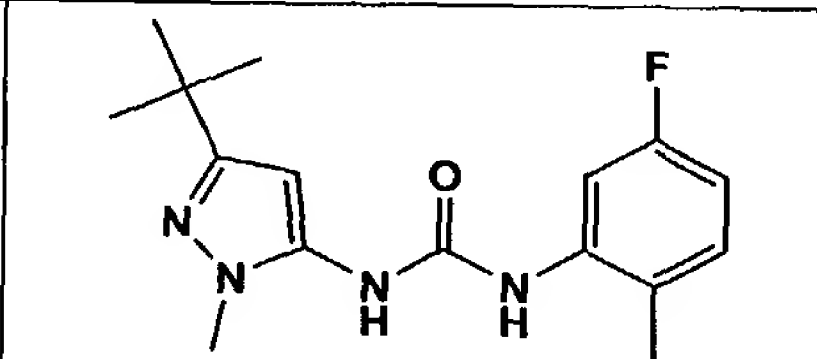
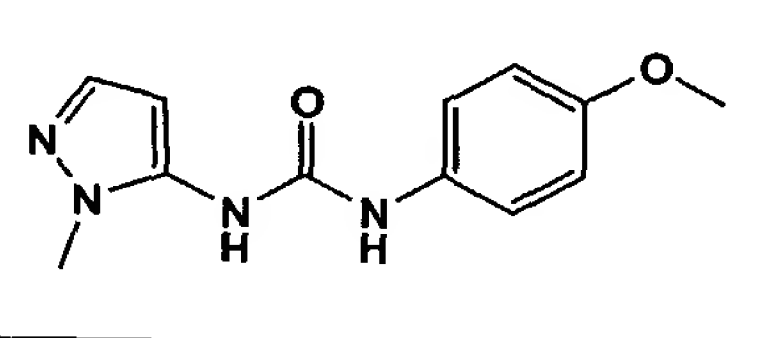
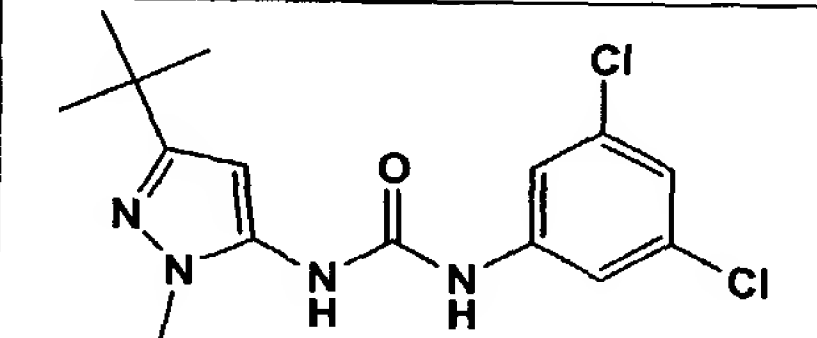
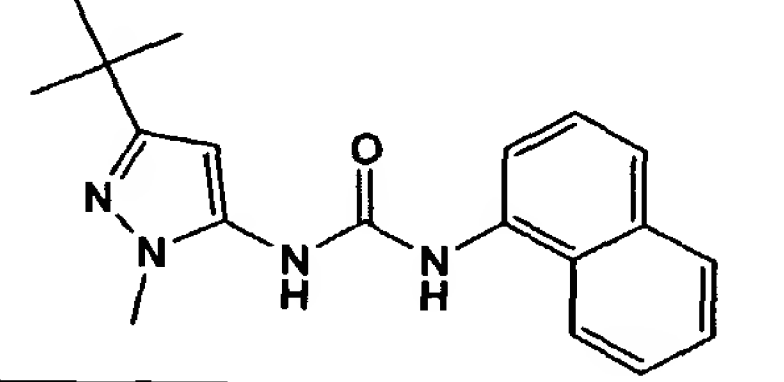
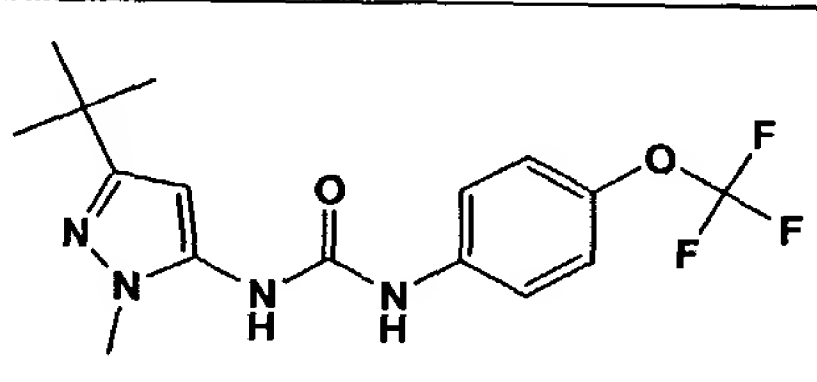
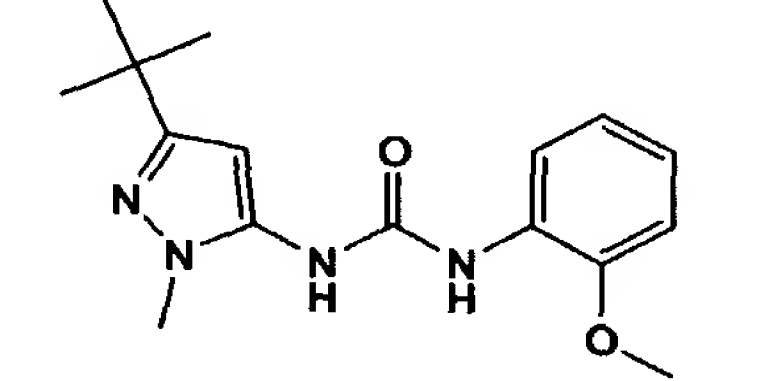
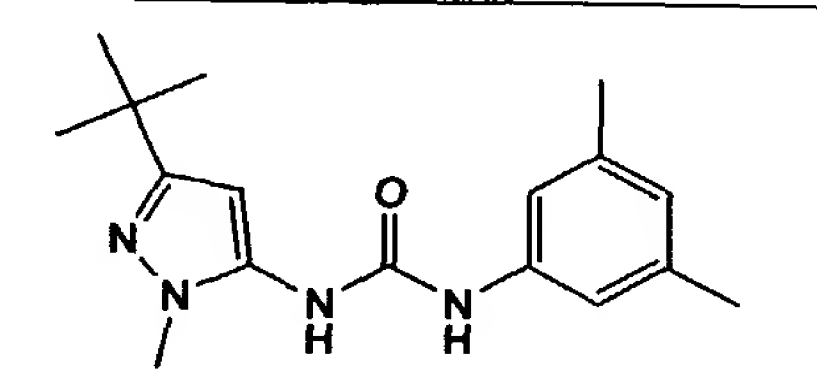


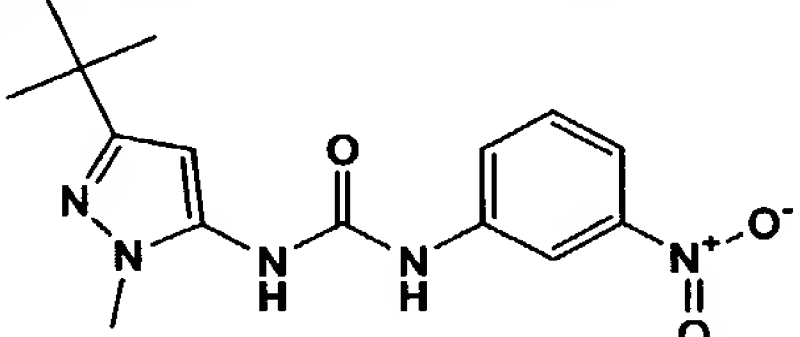
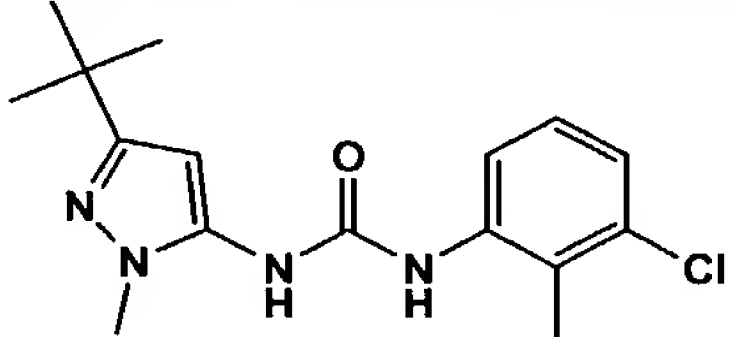
To a flask 3-tert-Butyl-5-isocyanato-1-p-tolyl-1H-pyrazole (242mg, 1eq) and substituted aniline (159mg, 1eq) was added and dissolved in toluene. The reaction was allowed to stir at 50°C for three hours. The solvent was removed and the mixture was purified by HPLC. Yield: 188mg (47%).

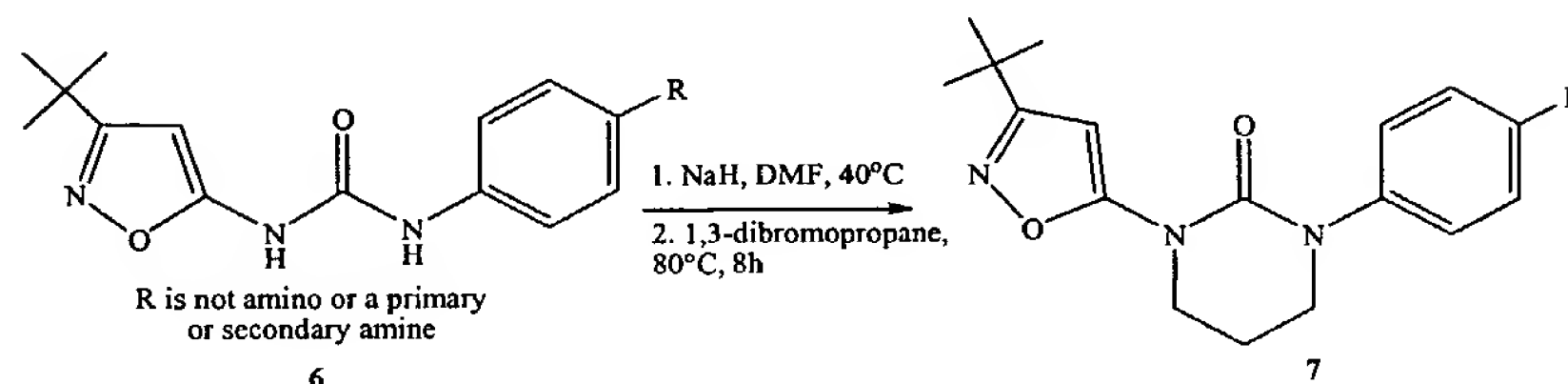
Compounds D2 through D22 were synthesized in a manner analogous to Compound D1 using similar starting materials and reagents. The structures are shown below in Table D:

Table D

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
D1		D2	
D3		D4	
D5		D6	

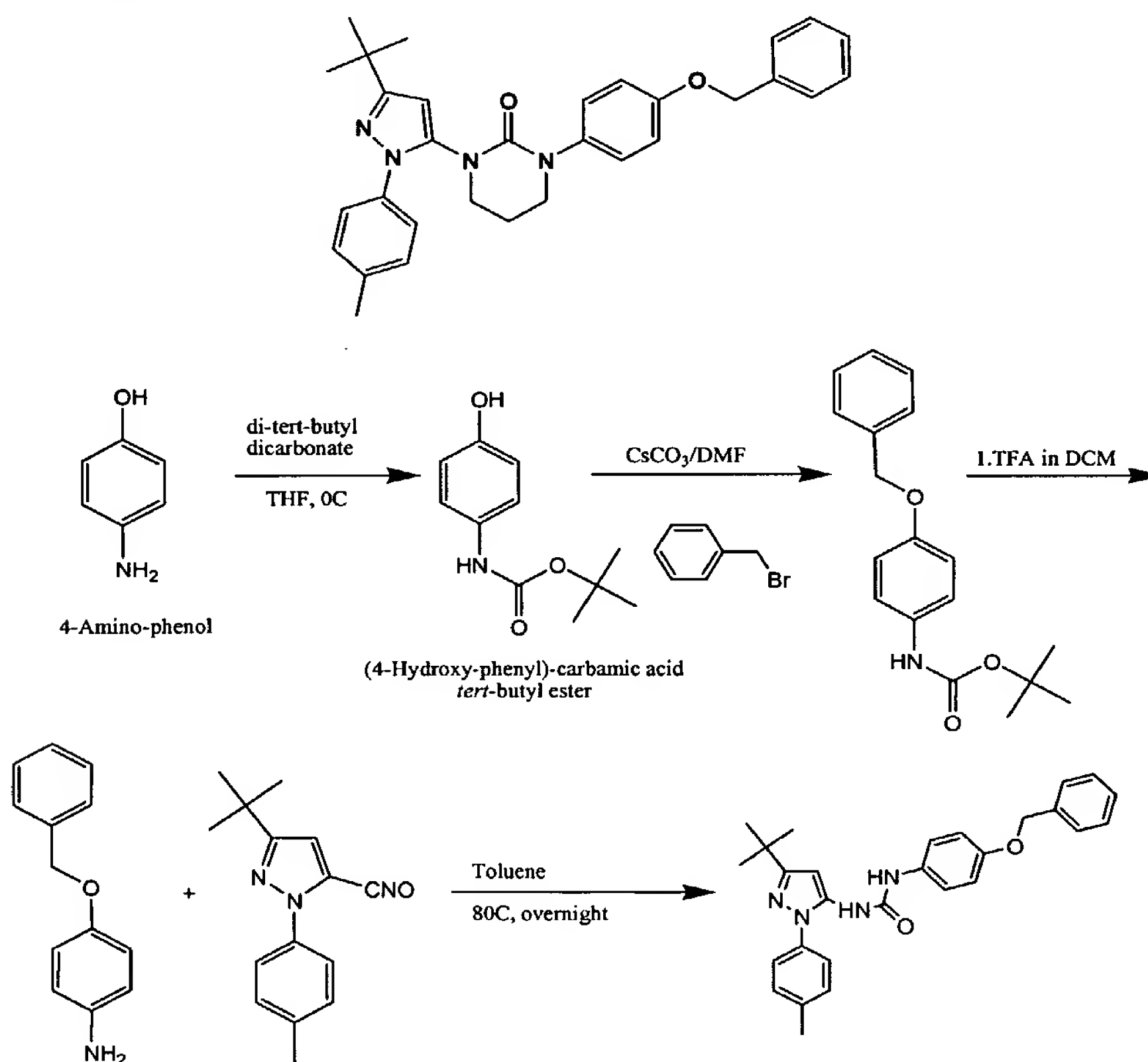
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
D7		D8	
D9		D10	
D11		D12	
D13		D14	
D15		D16	
D17		D18	
D19		D20	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
D21		D22	

Example E: Exemplary Synthesis of Cyclic Ureas

To the urea 6 is added NaH (2.5 eq) in DMF and the reaction is stirred at 40°C for 1 hour. Then 1 eq of 1,3-dibromopropane is added and the reaction heated to 80°C for 8 hours, then cooled, the solvent removed *in vacuo* and the product 7 purified by HPLC.

Synthesis of Compound E1: 3-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-1-(4-(benzyloxy)phenyl)-tetrahydropyrimidin-2(1H)-one



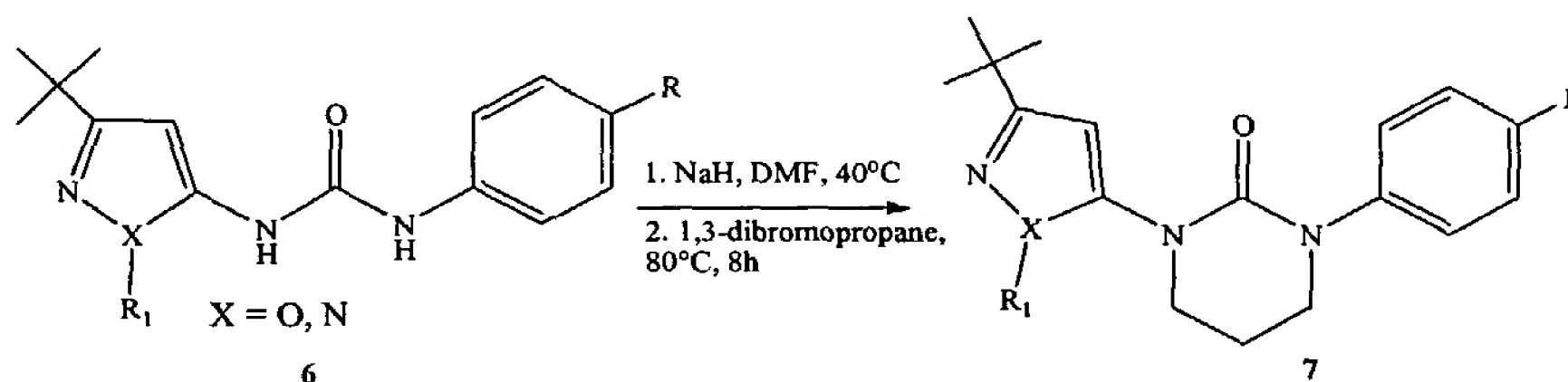
To a stirring solution of 4-aminophenol (1g, 1eq) in 20mL THF at 0°C di-tert-butyl dicarbonate (2g, 1eq) in 3mL THF was slowly added dropwise over 30 minutes. The reaction stirred at 0°C and allowed to warm to room temperature overnight. The solvent removed and diluted with ethyl acetate. It was then extracted with water three times, and the

organic layer was dried over magnesium sulfate. It was recrystallized in dichloromethane. Yield: 1.5g (79%).

Bocaminophenol (0.5g, 1eq), benzyl bromide (0.45g, 1eq), and cesium carbonate (1.94g, 2.5eq) was dissolved in 30mL dimethylformamide. The reaction was allowed to stir at 45°C overnight. The solvent was removed and dissolved in ethyl acetate and water. It was extracted with ethyl acetate three times. The organic layer was washed with 1N sodium hydroxide and dried with magnesium sulfate and solvent was removed. It was purified by column chromatography. Yield: 0.44g (58%).

[4-(benzyloxy)-phenyl]-carbamic acid tert-butyl ester (0.44g) was dissolved in 6mL dichloromethane and 2mL trifluoroacetic acid was added. The reaction stirred at room temperature for 1 hour. The excess trifluoroacetic acid was removed *in vivo*. Yield: 0.12g (42%).

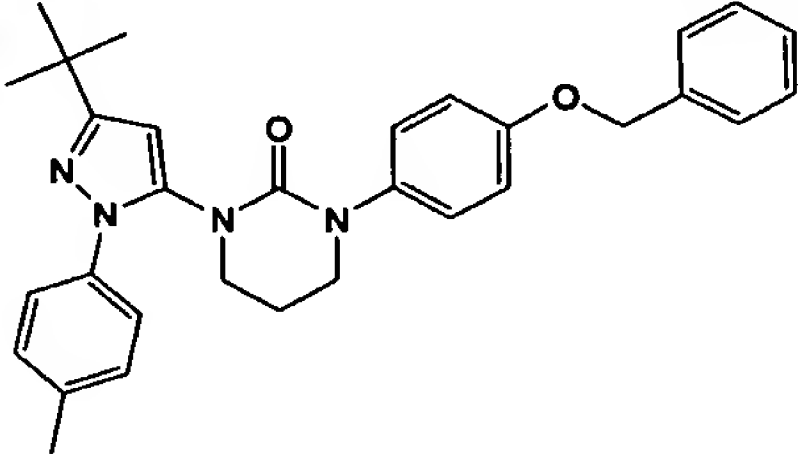
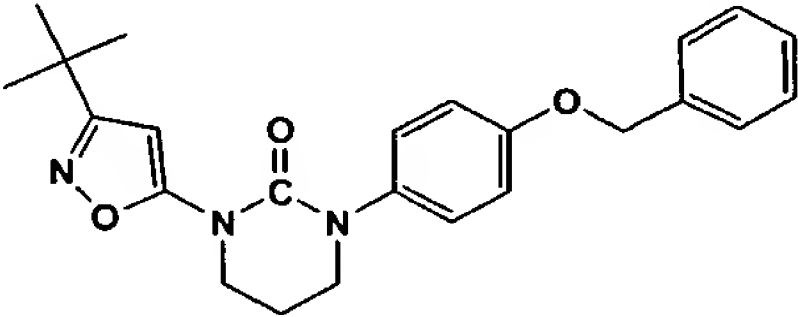
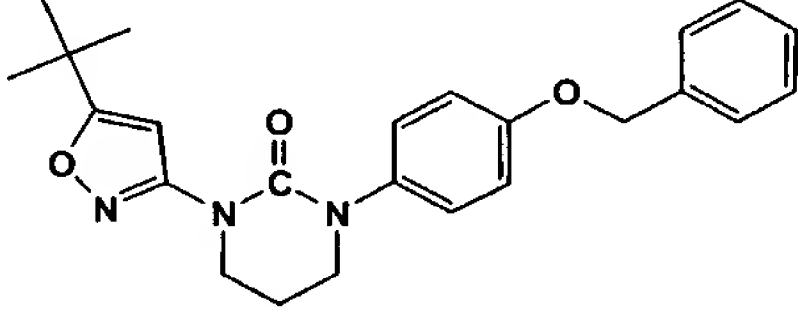
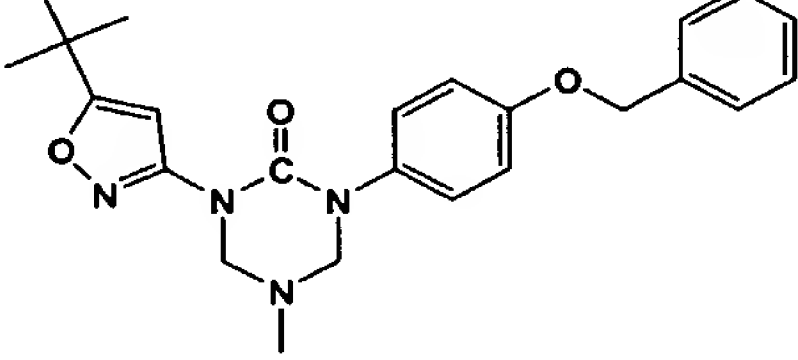
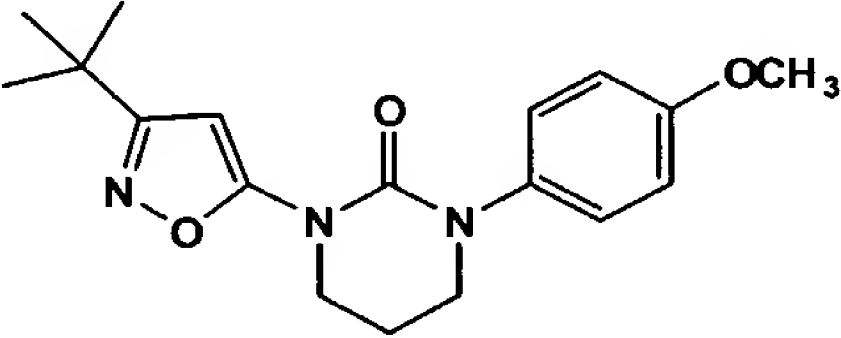
4-(benzyloxy)-phenylamine (0.12g, 1eq) was mixed with 5-tert-Butyl-2-p-tolyl-2H-pyrazole-3-carbonitrile N-oxide (0.9g 1eq) and dissolved in dry toluene. The reaction stirred at 80°C overnight. The solvent was removed and purified by HPLC. Yield: 85mg (31%)

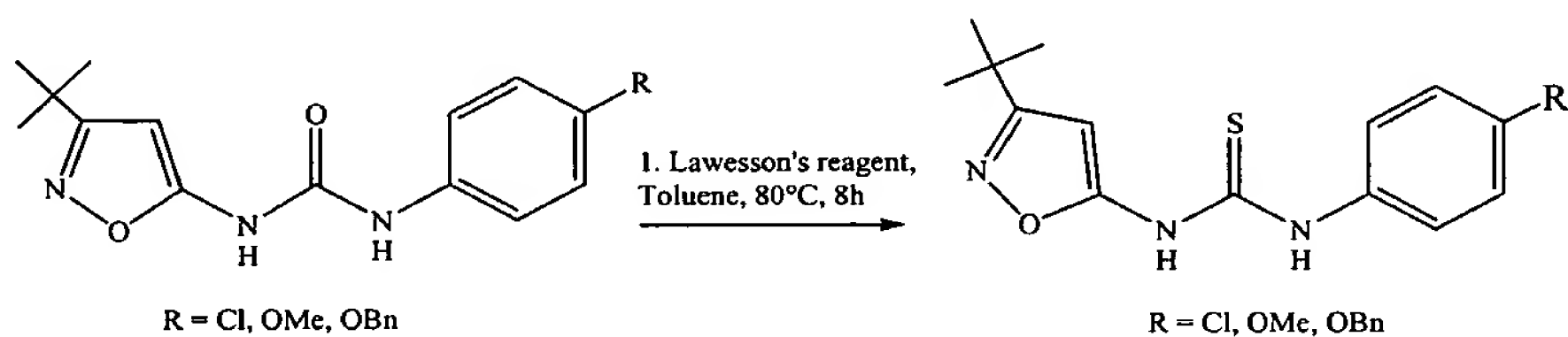


To 6 is added NaH (2.5 eq) in DMF and the reaction is stirred at 40°C for 1 hour. Then 1 eq of 1,3-dibromopropane is added and the reaction heated to 80°C for 8 hours, then cooled, the solvent removed *in vacuo* and the product 7 purified by HPLC.

Compounds E2 through E5 were synthesized in a manner analogous to Compound E1 using similar starting materials and reagents. The structures are shown below in Table E:

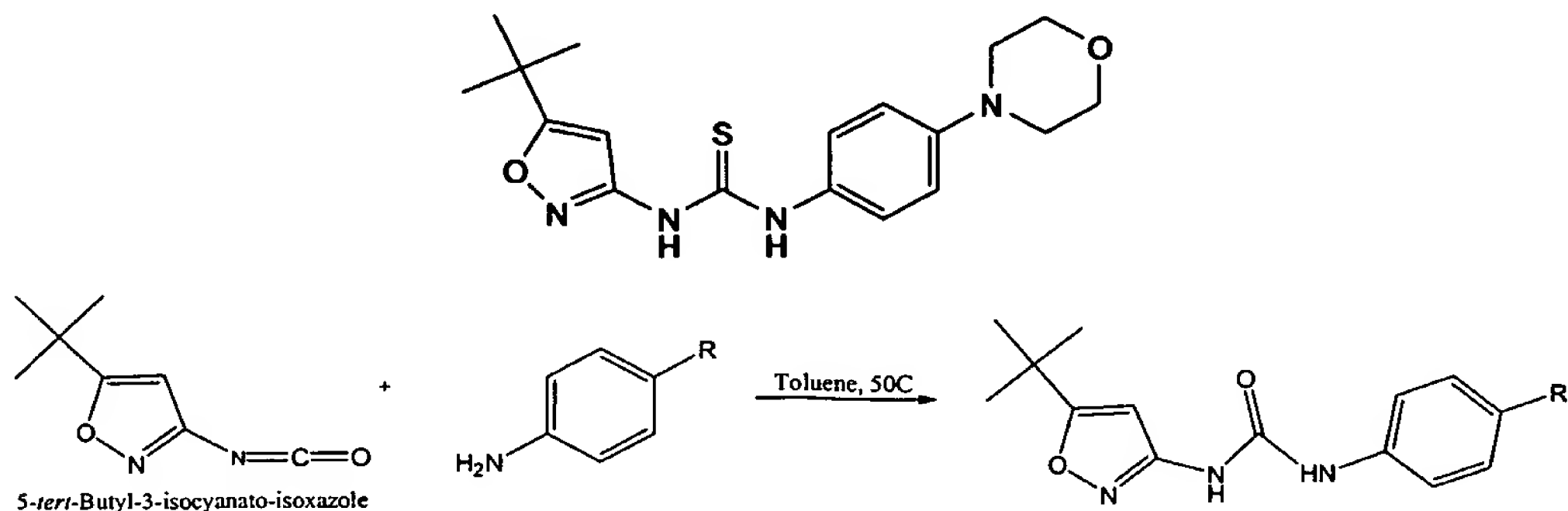
Table E

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
E1		E2	
E3		E4	
E5			

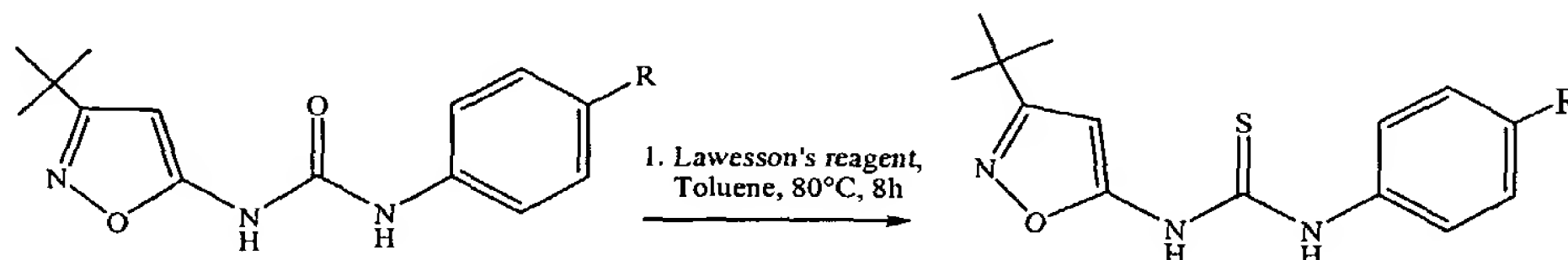
Example F: Conversion of Ureas to Thioureas

Lawesson's reagent is added to starting urea in toluene and the reaction heated to 100°C for 8 hours, then cooled, the solvent removed *in vacuo* and the thiourea purified by HPLC.

Synthesis of Compound F1: 1-(5-tert-butylisoxazol-3-yl)-3-(4-morpholinophenyl)thiourea



To a flask 5-tert-Butyl-3-isocyanato-isoxazole (242mg, 1eq) and substituted aniline (159mg, 1eq) was added and dissolved in toluene. The reaction was allowed to stir at 50°C for three hours. The solvent removed and the mixture was purified by HPLC. Yield: 188mg (47%)

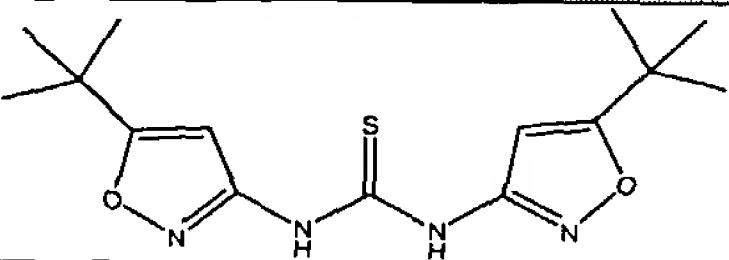


Lawesson's reagent is added to starting urea in toluene and the reaction heated to 100°C for 8 hours, then cooled, the solvent removed *in vacuo* and the thiourea purified by HPLC.

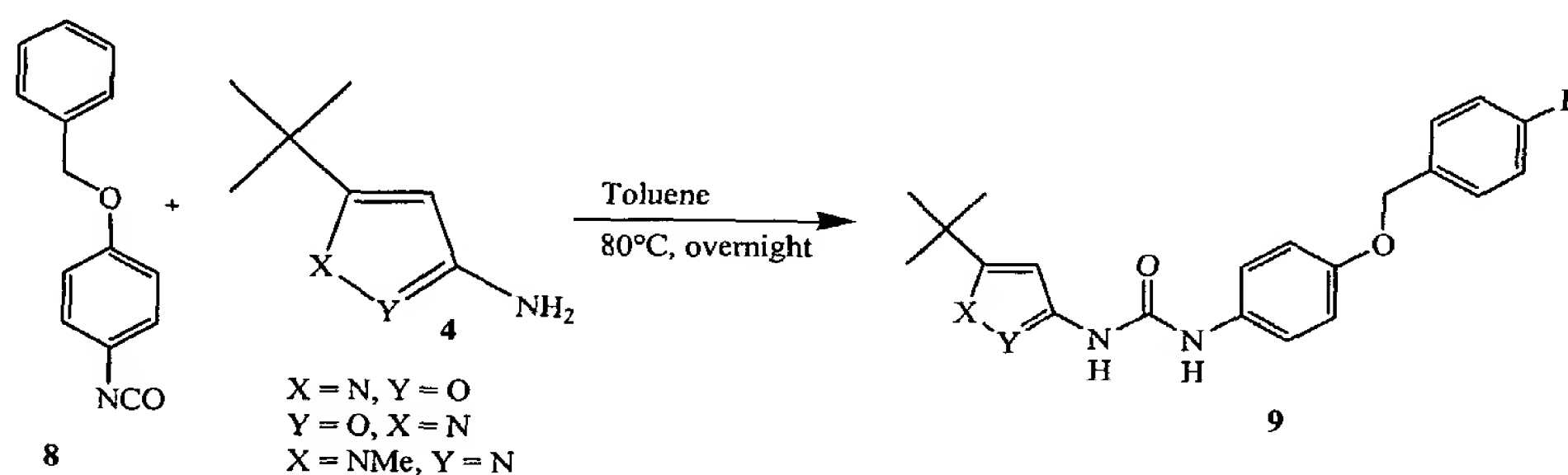
Compounds F2 through F9 were synthesized in a manner analogous to Compound F1 using similar starting materials and reagents. The structures are shown below in Table F:

Table F

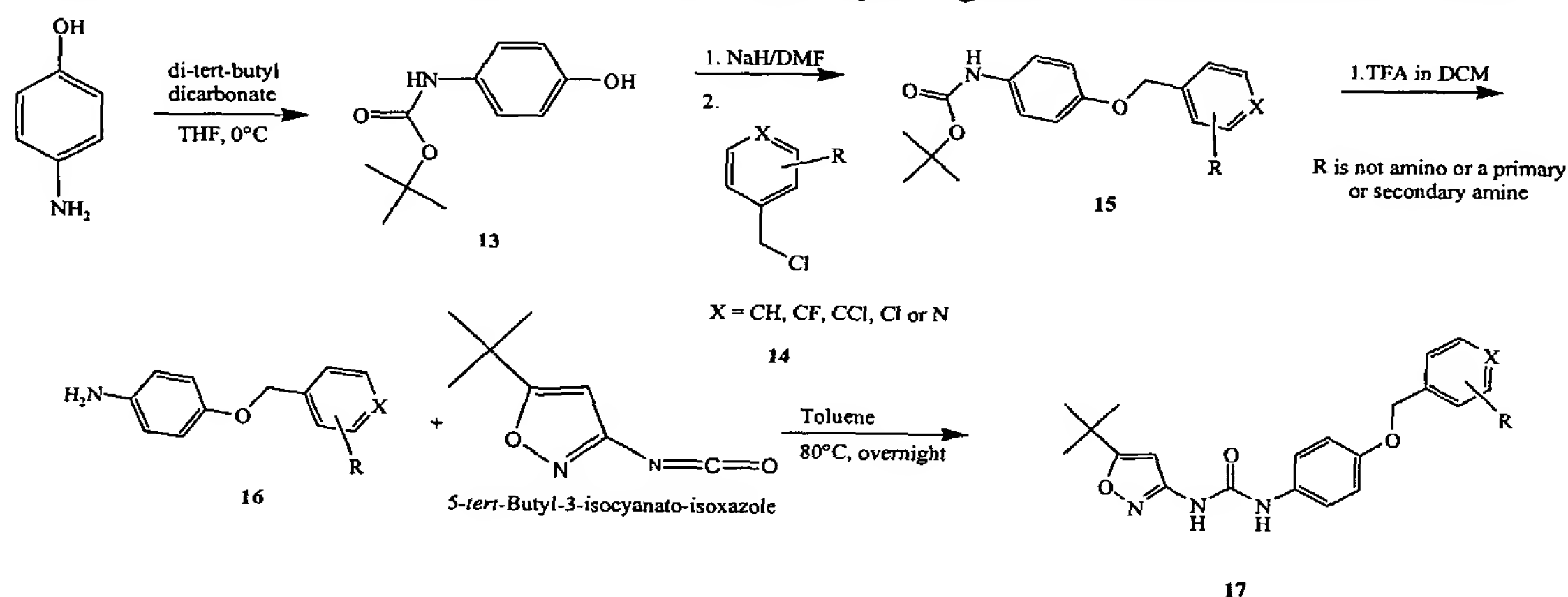
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
F1 8		F2	
F3		F4	
F5		F6	
F7		F8	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
F9			

Example G: Exemplary Synthesis of Ureas with Ether Linkers



To a stirring solution of the amine 4 (1 eq) in toluene at room temperature is added the isocyanate 8 and heated at 80°C overnight. The solvent is removed, and the product 9 is purified by HPLC. Compound C, compound A, compound B, compound D and other compounds in the benzoxo series were made by the general method described above.



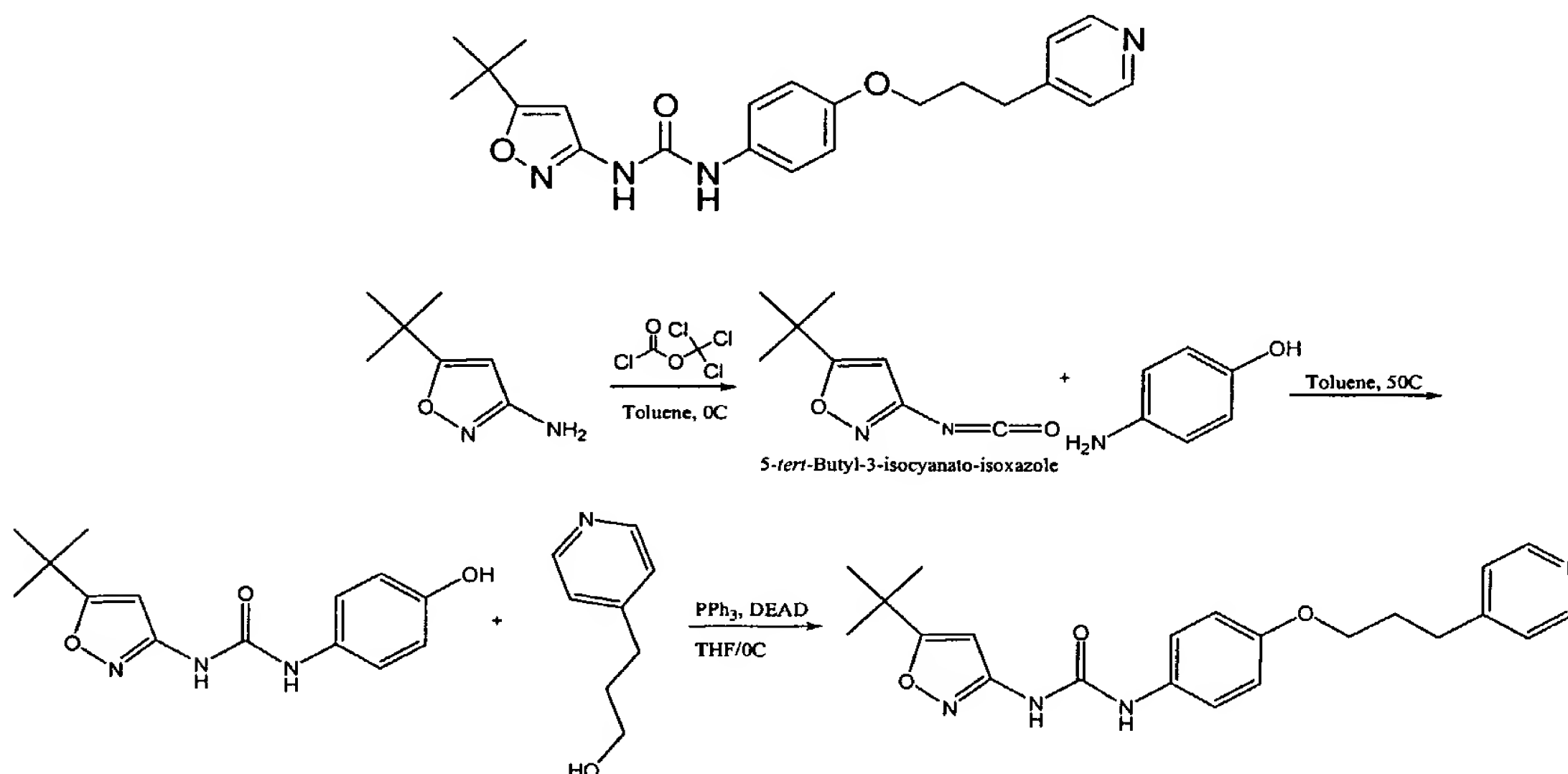
To a stirring solution of 4-aminophenol (1 eq) in THF at 0°C di-tert-butyl dicarbonate (1 eq) in THF was slowly added dropwise over 30 minutes. The reaction stirred at 0°C and allowed to warm to room temperature overnight. The solvent removed and diluted with ethyl acetate. It was then extracted with water three times, and the organic layer was dried over magnesium sulfate. It was recrystallized in dichloromethane.

To a stirring solution of sodium hydride (1.2 eq) in DMF, the Boc-aminophenol (1 eq) was added dropwise at 0°C and stirred to room temperature for one hour. Then the substituted benzyl halide (1 eq) in THF was added dropwise at 0°C. The reaction was allowed to stir at 40°C overnight. The solvent was removed and dissolved in ethyl acetate and water. It was extracted with ethyl acetate three times. The organic layer was washed with 1N sodium hydroxide and dried with magnesium sulfate and solvent was removed. It was purified by column chromatography.

The protected substituted benzyloxylaniline was dissolved in dichloromethane and trifluoroacetic acid was added. The reaction stirred at room temperature for 1 hour. The excess trifluoroacetic acid was removed *in vivo*.

The substituted benzyloxylaniline (1 eq) was mixed with 5-tert-Butyl-3-isocyanato-isoxazole (1 eq) and dissolved in dry toluene. The reaction stirred at 80°C overnight. The solvent was removed and purified by HPLC.

Synthesis of Compound G1: 1-(4-(3-(pyridin-4-yl)propoxy)phenyl)-3-(5-tert-butylisoxazol-3-yl)urea

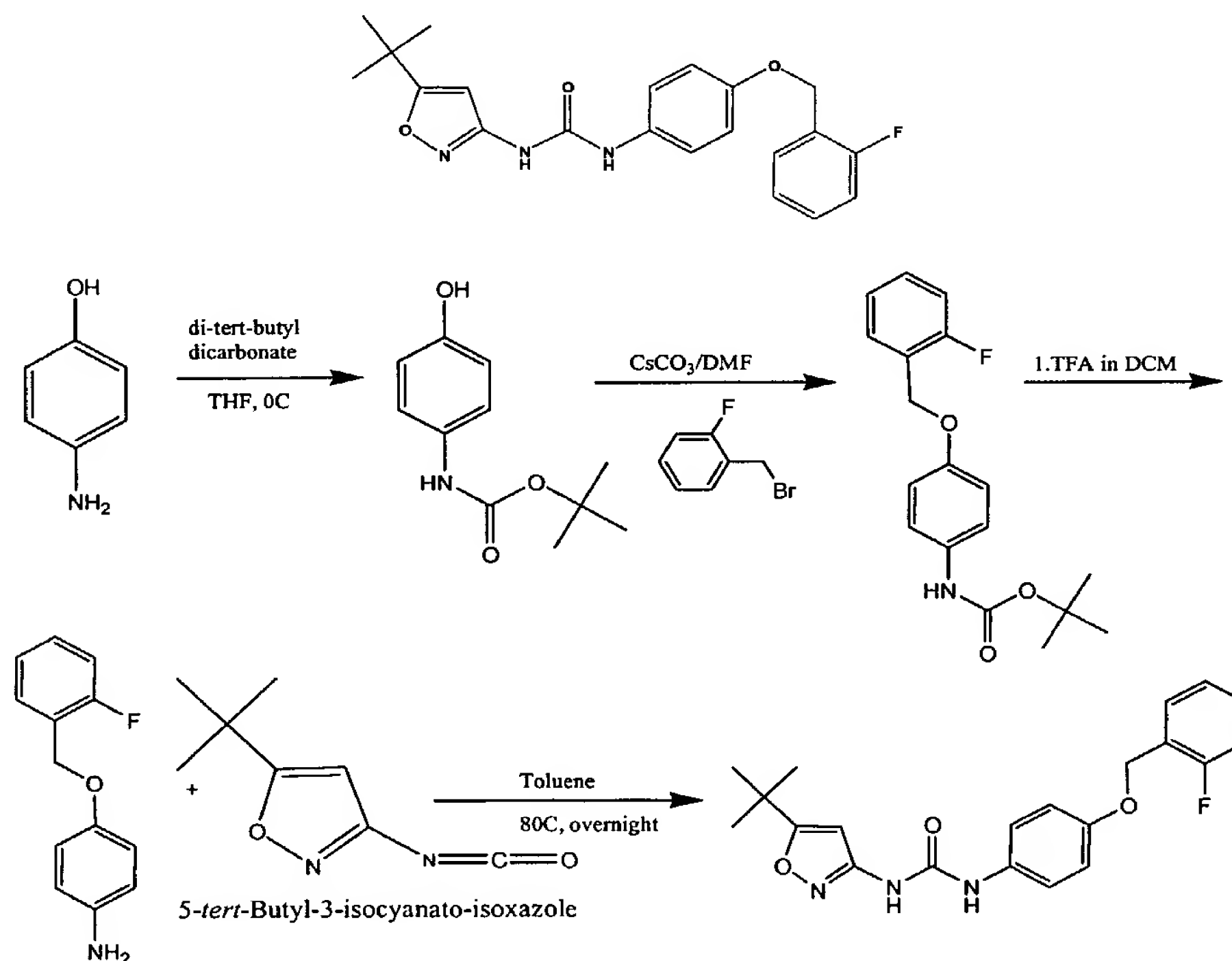


To a stirring solution of 5-tert-Butyl-isoxazol-3-ylamine (250mg, 1eq) in dry toluene at 0°C trichloromethyl chloroformate (1.1eq) was added dropwise. The reaction stirred at 0°C and allowed to warm to room temperature overnight. The solvent was removed and the mixture was recrystallized in ethyl acetate. The solid was filtered off and washed with cold ethyl acetate. Yield: 242mg (83%).

To a flask 5-tert-Butyl-3-isocyanato-isoxazole (242mg, 1eq) and 4-aminophenol (159mg, 1eq) was added and dissolved in toluene. The reaction was allowed to stir at 50°C for three hours. The solvent removed and the mixture was purified by HPLC. Yield: 188mg (47%), LC/MS [MH⁺] 276.

In a dry flask flushed with nitrogen gas 1-(5-tert-Butyl-isoxazol-3-yl)-3-(4-hydroxy-phenyl)-urea (100mg, 1eq), 3-Pyridin-4-yl-propan-1-ol (200mg, 1eq) and triphenylphosphine (143mg, 1.5eq) was added and then dissolved with THF. The flask was cooled to 0°C and diethyl azodicarboxylate (95mg, 1.5eq) was added dropwise. The reaction stirred overnight at room temperature. The THF was removed and the mixture was purified by HPLC. Yield: 26mg (18%), LC/MS [MH⁺] 395.

Synthesis of Compound G12: 1-(4-(2-fluorobenzyloxy)phenyl)-3-(5-tert-butylisoxazol-3-yl)urea



To a stirring solution of 4-aminophenol (1g, 1eq) in 20mL THF at 0°C di-tert-butyl dicarbonate (2g, 1eq) in 3mL THF was slowly added dropwise over 30 minutes. The reaction stirred at 0°C and allowed to warm to room temperature overnight. The solvent removed and diluted with ethyl acetate. It was then extracted with water three times, and the

organic layer was dried over magnesium sulfate. It was recrystallized in dichloromethane. Yield: 1.5g (79%).

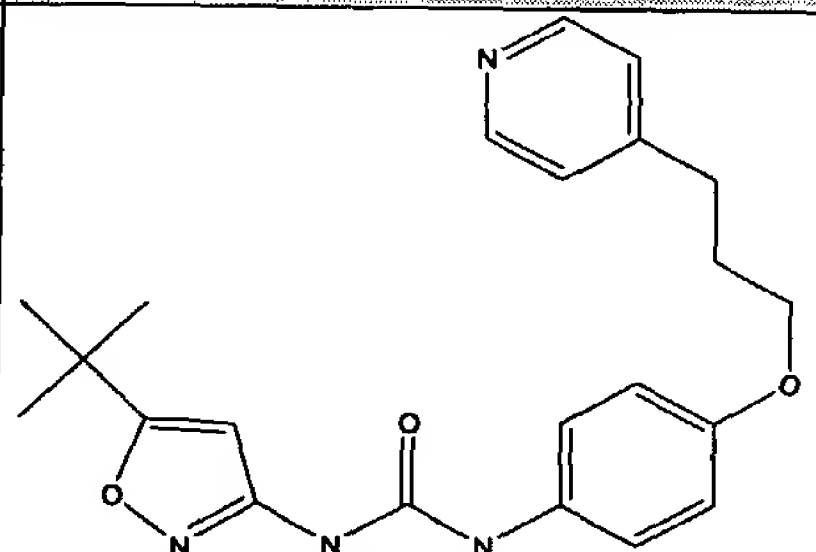
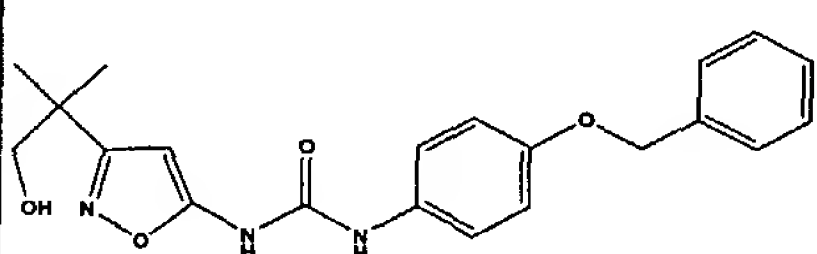
Bocaminophenol (0.5g, 1eq), 2-fluorobenzyl bromide (0.45g, 1eq), and cesium carbonate (1.94g, 2.5eq) was dissolved in 30mL dimethylformamide. The reaction was allowed to stir at 45°C overnight. The solvent was removed and dissolved in ethyl acetate and water. It was extracted with ethyl acetate three times. The organic layer was washed with 1N sodium hydroxide and dried with magnesium sulfate and solvent was removed. It was purified by column chromatography. Yield: 0.44g (58%).

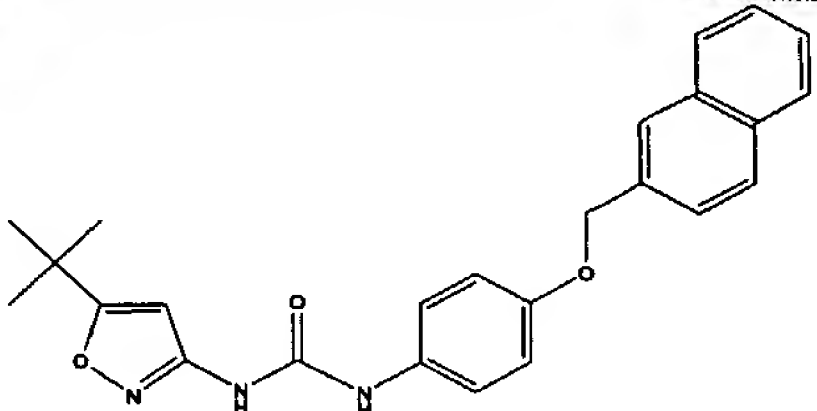
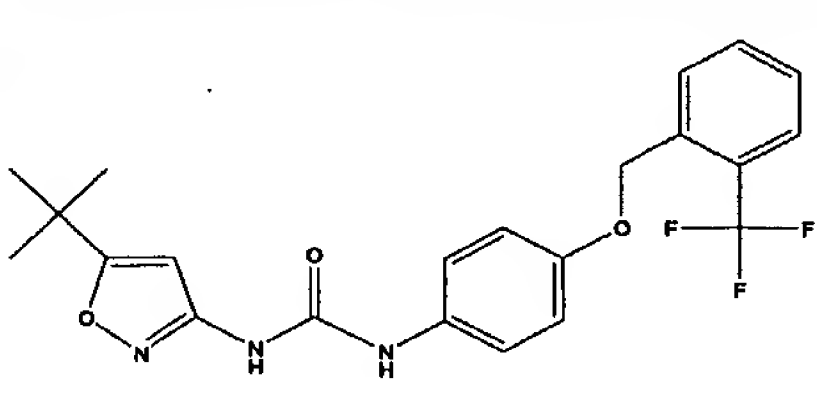
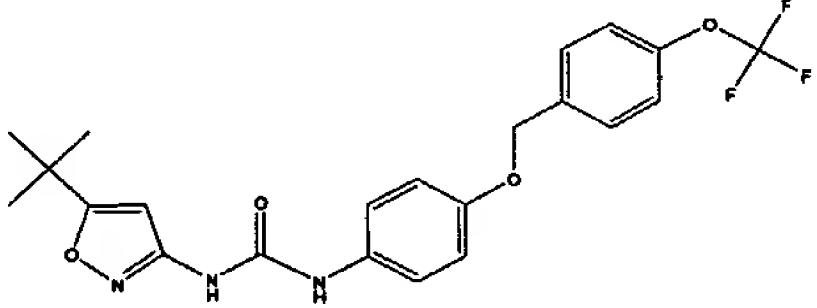
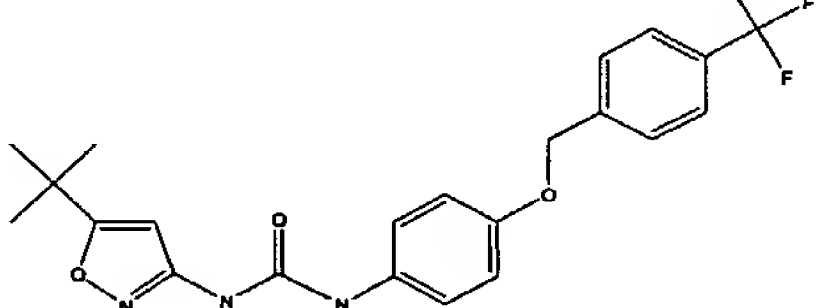
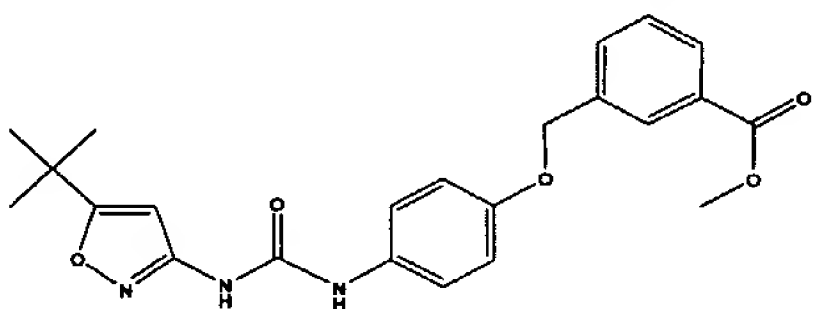
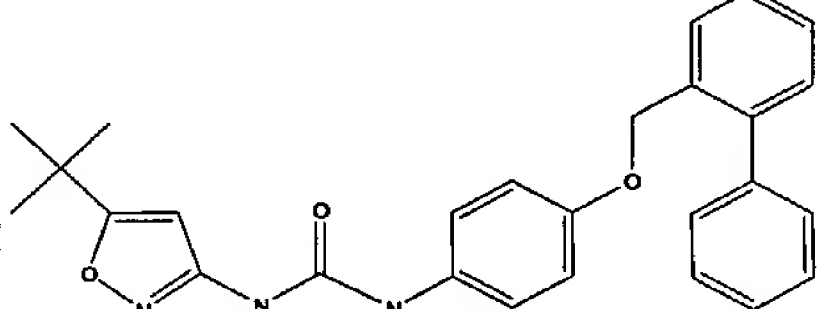
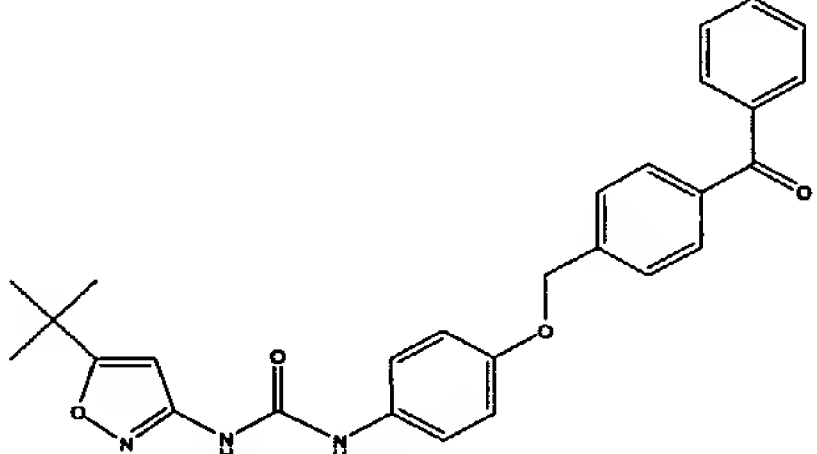
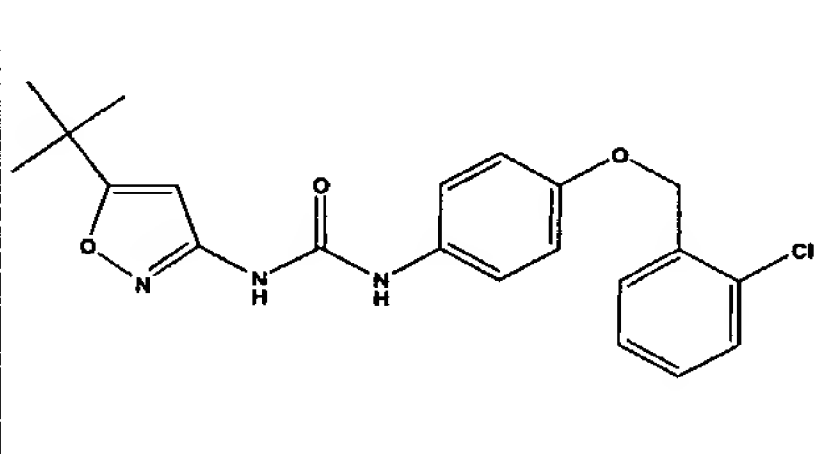
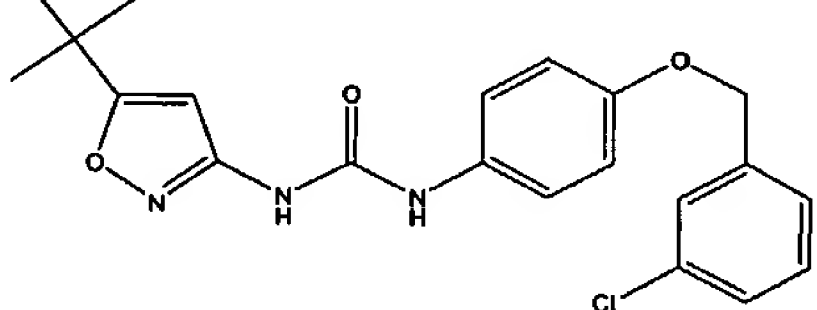
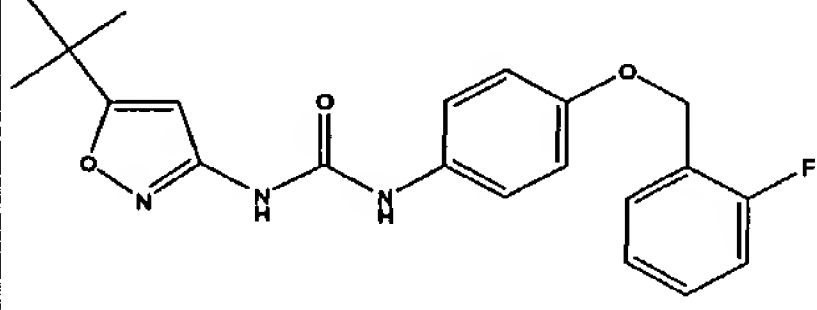
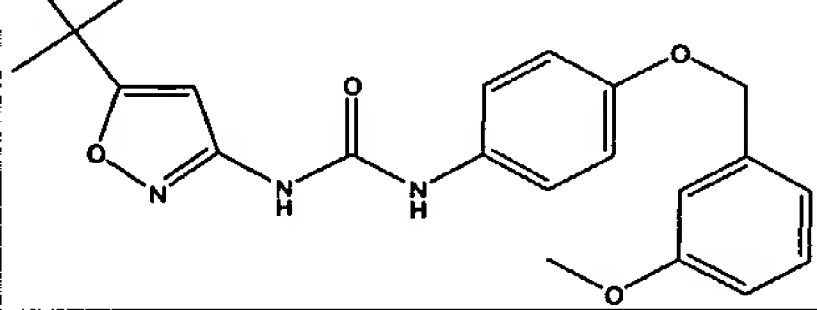
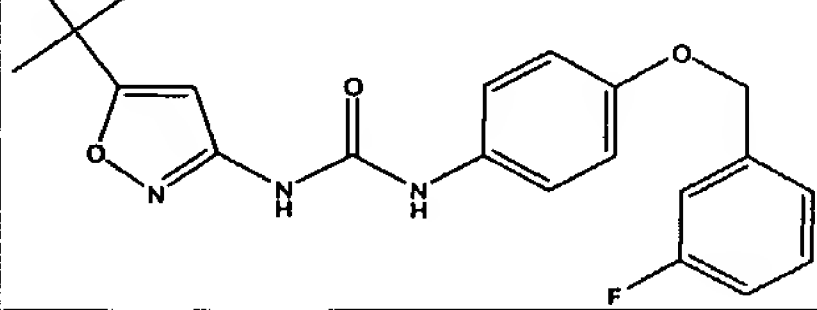
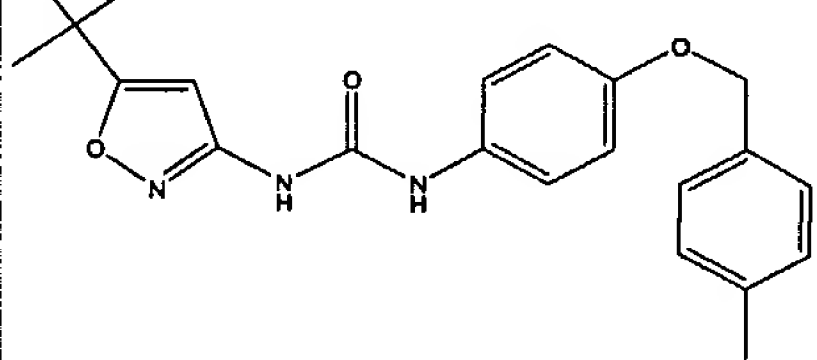
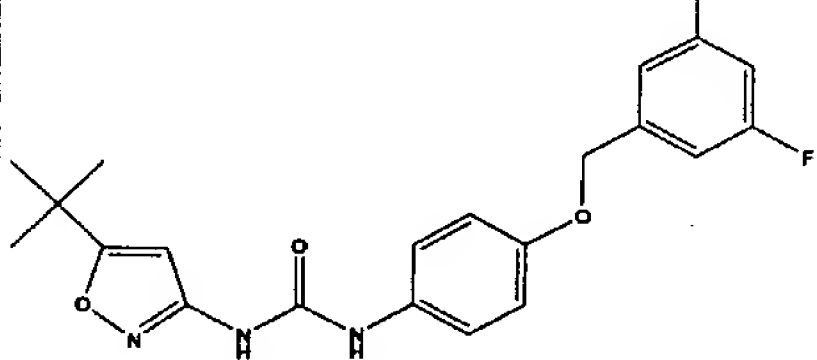
[4-(2-Fluoro-benzyloxy)-phenyl]-carbamic acid tert-butyl ester (0.44g) was dissolved in 6mL dichloromethane and 2mL trifluoroacetic acid was added. The reaction stirred at room temperature for 1 hour. The excess trifluoroacetic acid was removed in vivo. Yield: 0.12g (42%), LC/MS $[MH^+]$ 218.

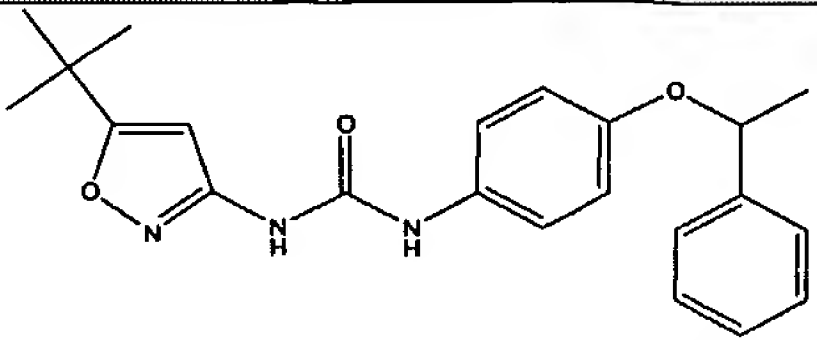
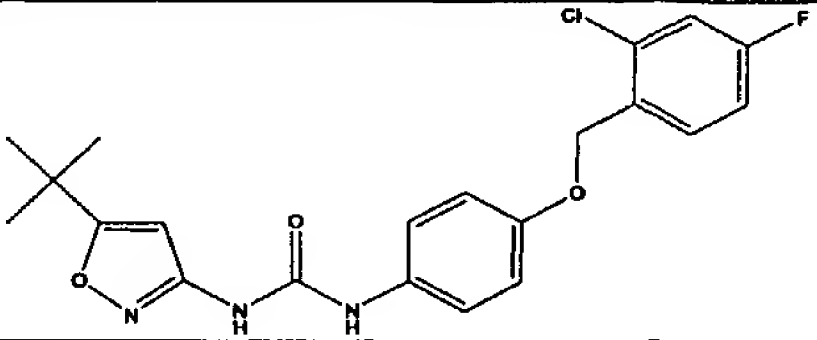
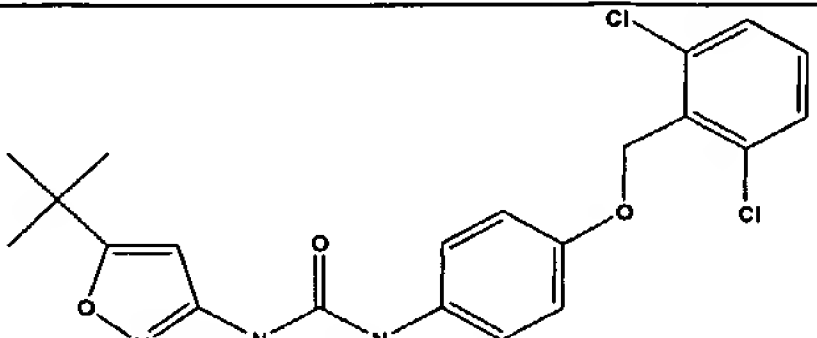
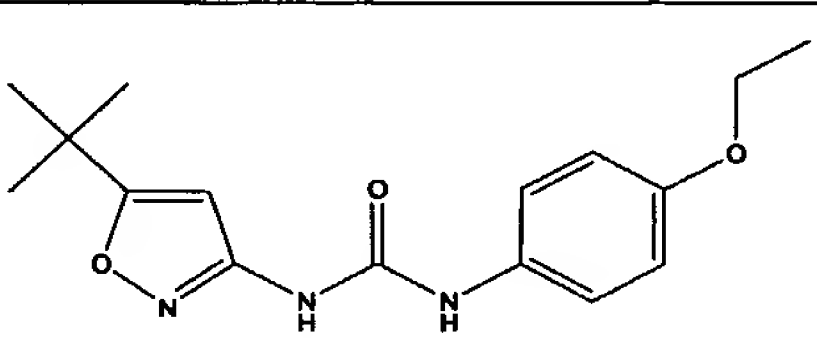
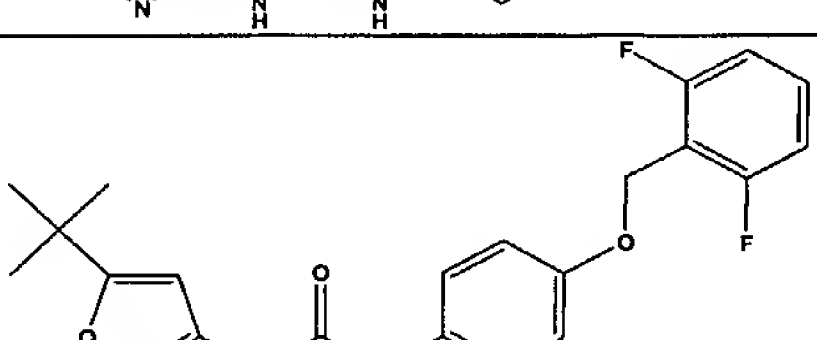
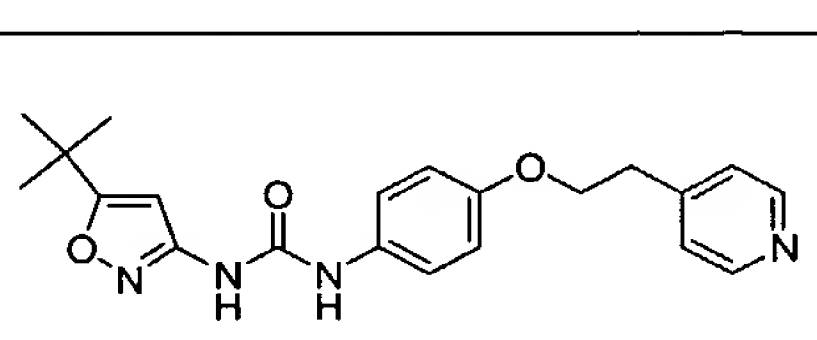
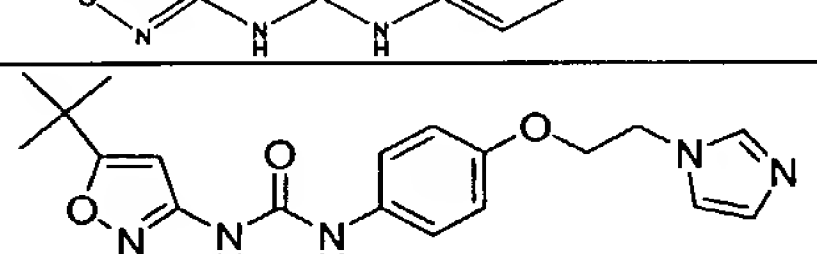
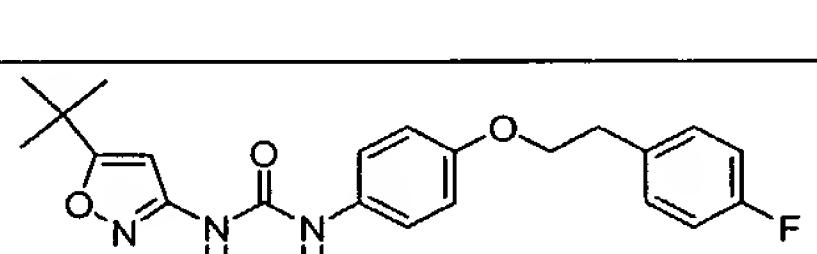
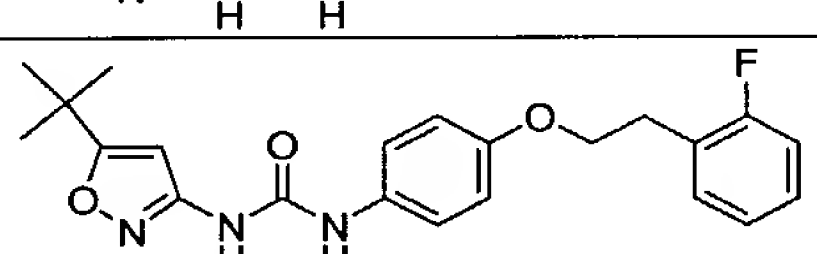
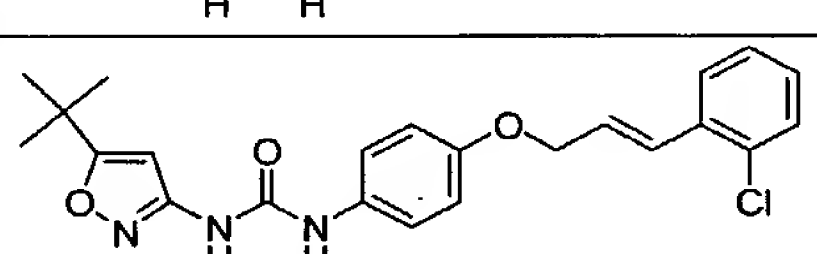
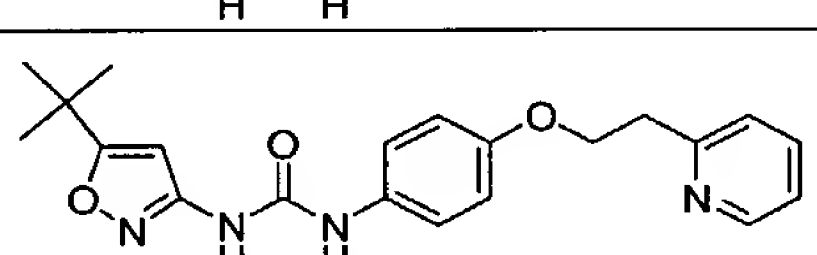
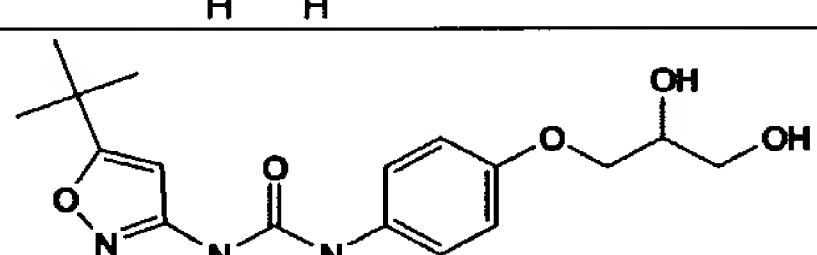
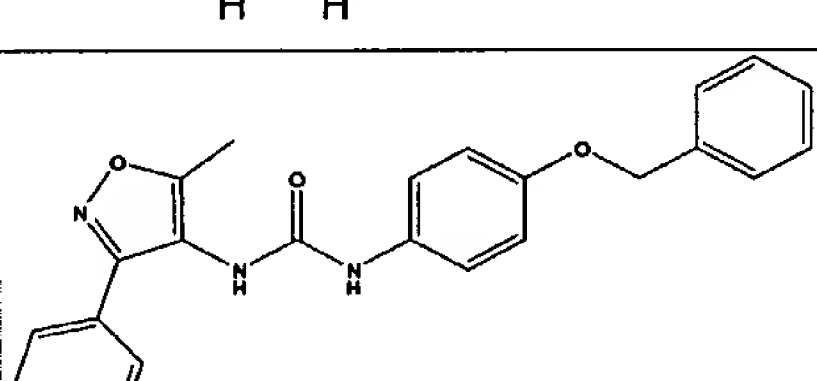
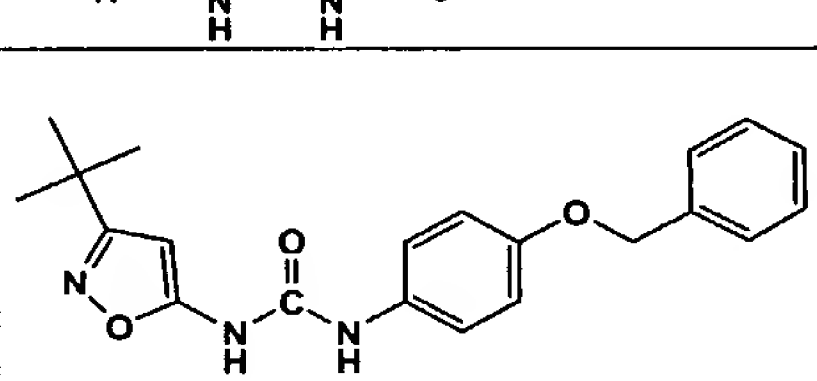
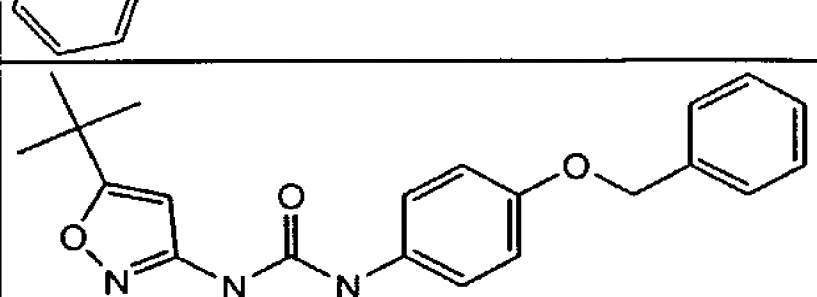
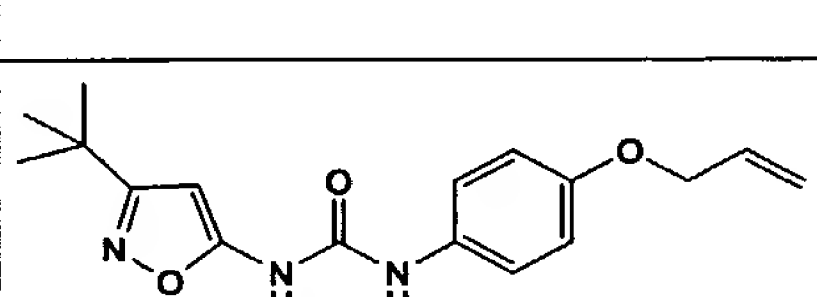
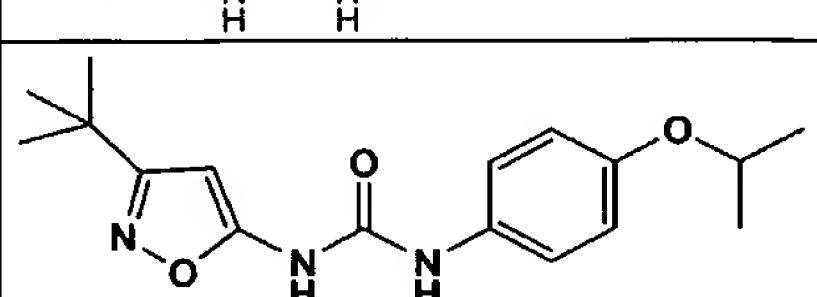
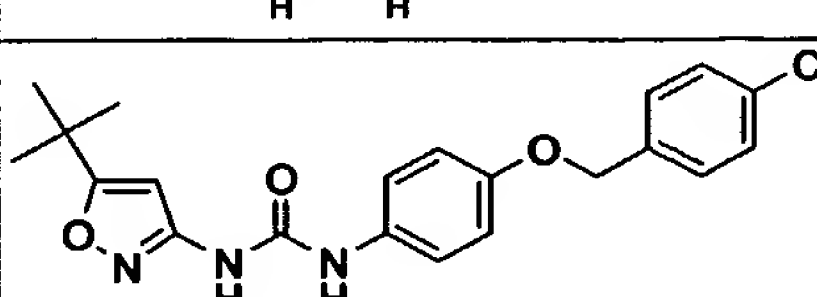
4-(2-Fluoro-benzyloxy)-phenylamine (0.12g, 1eq) was mixed with 5-tert-Butyl-3-isocyanato-isoxazole (0.9g 1eq) and dissolved in dry toluene. The reaction stirred at 80°C overnight. The solvent was removed and purified by HPLC. Yield: 85mg (31%), LC/MS $[MH^+]$ 384.

Compounds G2 through G57 were synthesized in a manner analogous to Compound G1 and G12 using similar starting materials and reagents. The structures are shown below in Table G:

Table G

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
G1		G2	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
G3		G4	
G5		G6	
G7		G8	
G9		G10	
G11		G12	
G13		G14	
G15		G16	

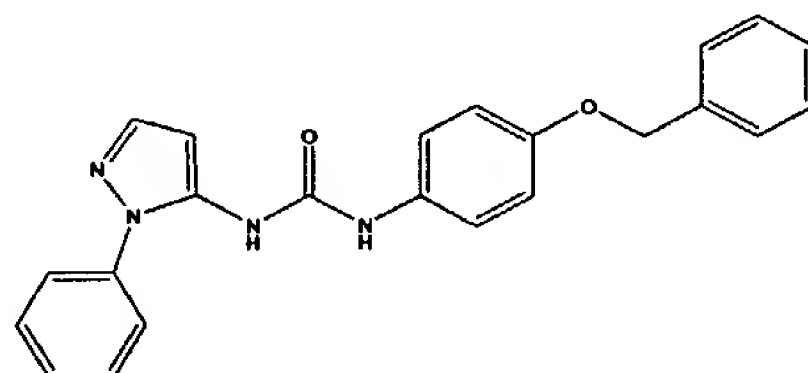
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
G17		G18	
G19		G20	
G21		G22	
G23		G24	
G25		G26	
G27		G28	
G29		G30	
G31		G32	
G33		G34	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
G35		G36	
G37		G38	
G39		G40	
G42		G44	
G46		G48	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
G49		G50	
G51		G52	
G53		G54	
G55		G56	
G57			

Example H: Exemplary Synthesis of Ureas with Ether Linkers

Synthesis of Compound H1: 1-(4-(benzyloxy)phenyl)-3-(1-phenyl-1H-pyrazol-5-yl)urea



Compounds H1 through H10 were synthesized in a manner analogous to compound G1.
Compounds H11 through H17 were synthesized in a manner analogous to Compound A1
using similar starting materials and reagents. The structures are shown below in Table H:

5

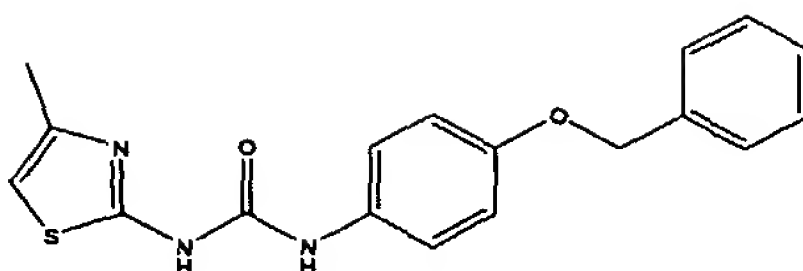
Table H

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
H1		H2	
H3		H4	
H5		H6	
H7		H8	
H9		H10	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
H11		H12	
H13		H14	
H15		H16	
H17			

Example I: Exemplary Synthesis of Ureas with Ether Linkers

Synthesis of Compound II: 1-(4-(benzyloxy)phenyl)-3-(4-methylthiazol-2-yl)urea



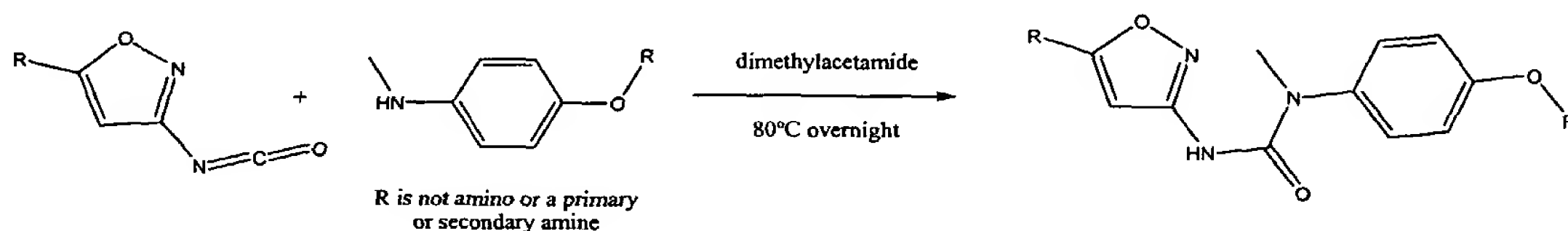
Compounds I1 through I4 were synthesized in a manner analogous to Compound G1 using similar starting materials and reagents. The structures are shown below in Table I:

Table I

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
I1		I2	
I3		I4	

5

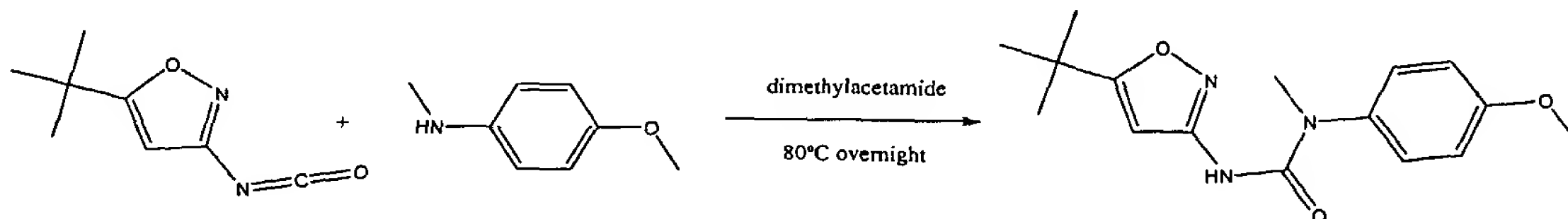
Example J: Synthesis of N-Substituted Ureas



A solution of an isoxazole-3-isocyanate in dimethylacetamide is added to a solution of 4-alkoxy-N-alkylbenzenamine in dimethylacetamide, and the mixture is heated at 80°C overnight. After cooling to room temperature, 20 ml water is added and the mixture is extracted with 3x30 ml EtOAc. The combined organic phases are washed with brine, dried over magnesium sulfate, and evaporated. Purification of the product is accomplished by flash chromatography (silica gel, hexanes, 0-50% EtOAc).

10

Synthesis of Compound J1: 1-(5-tert-butylisoxazol-3-yl)-3-(4-methoxyphenyl)-3-methylurea



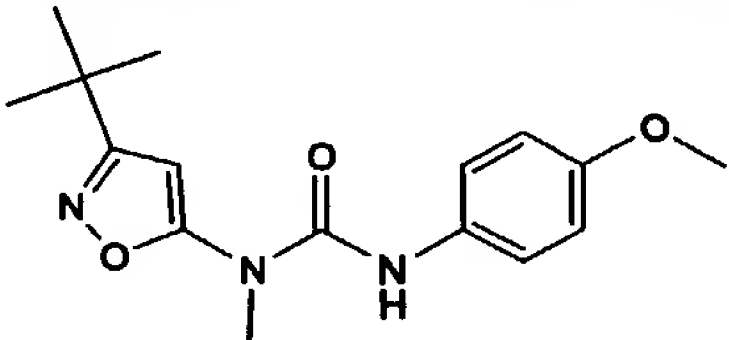
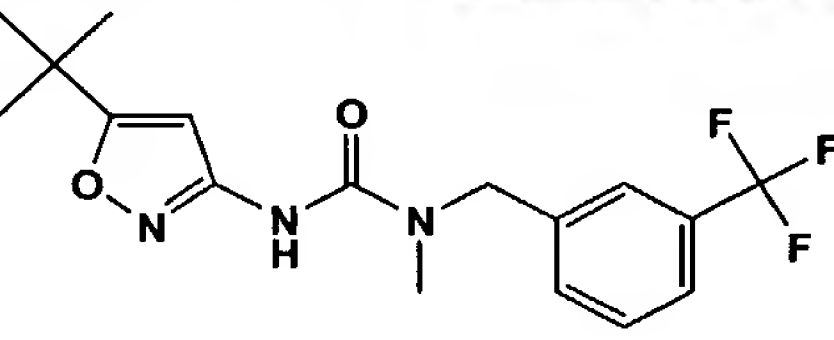
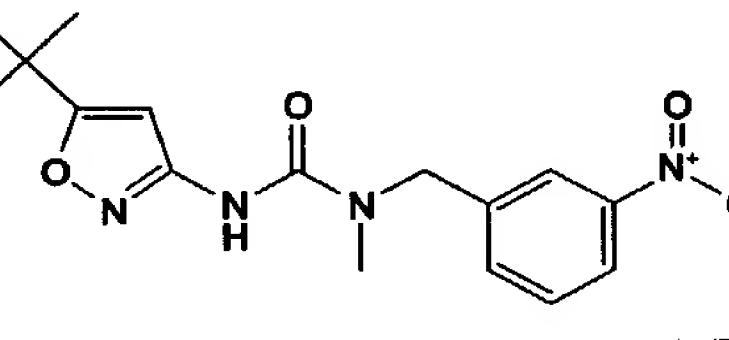
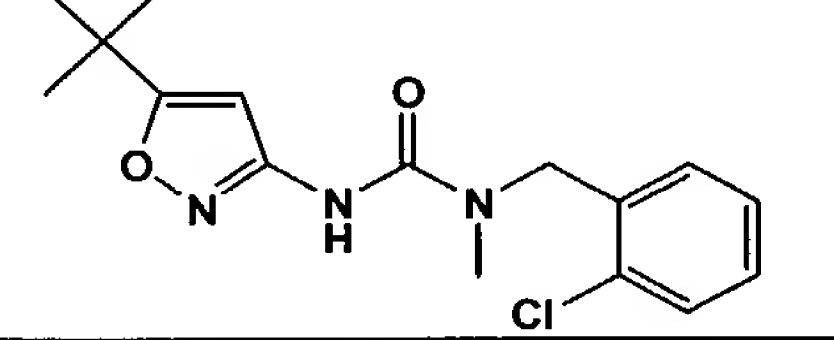
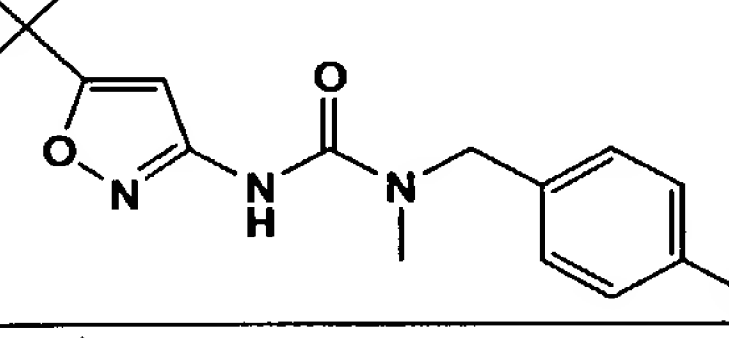
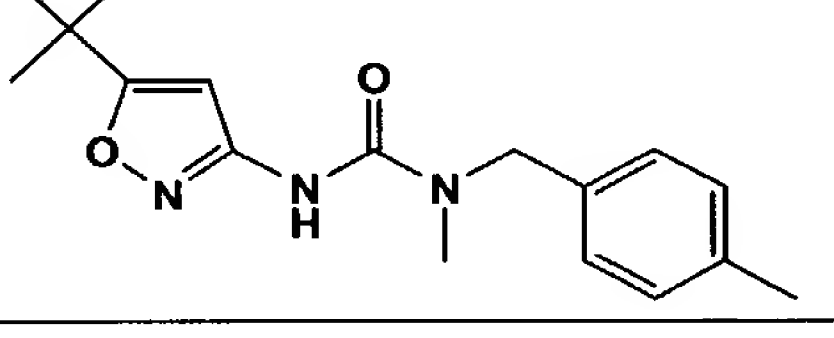
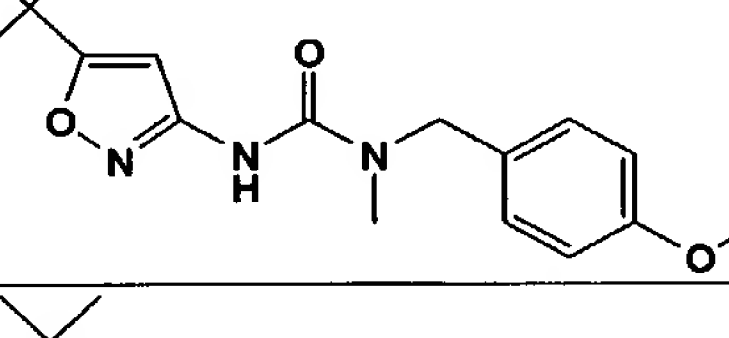
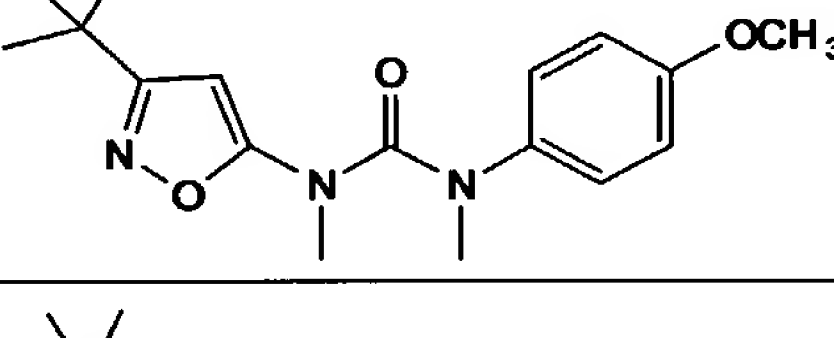
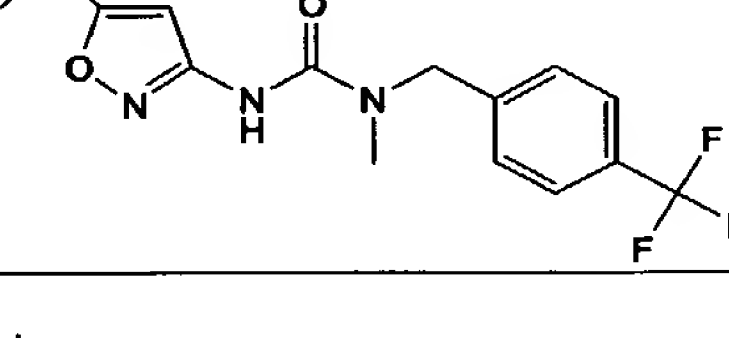
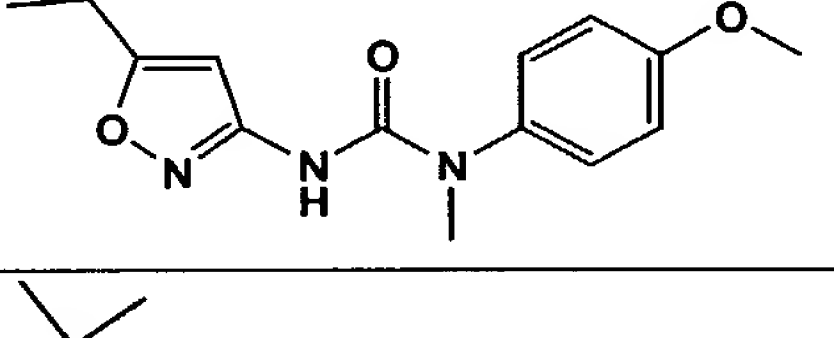
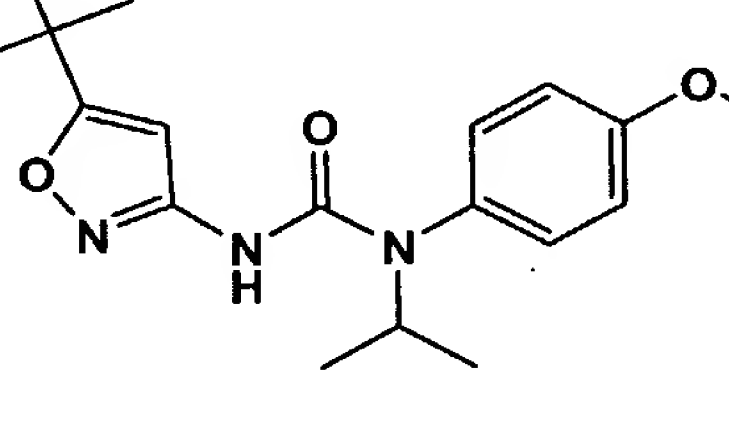
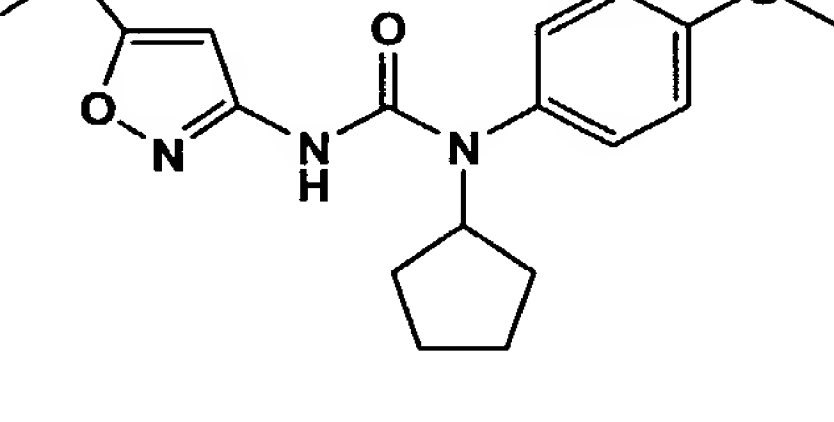
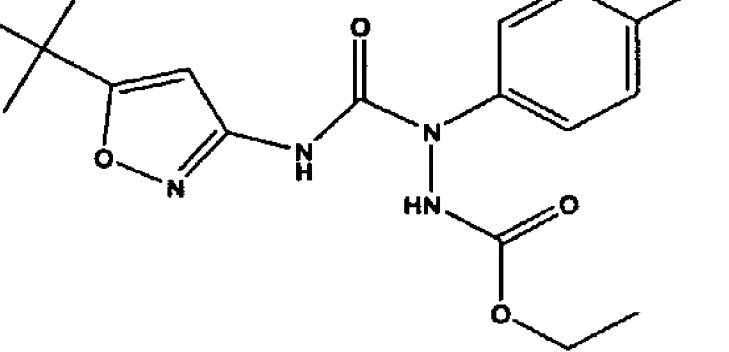
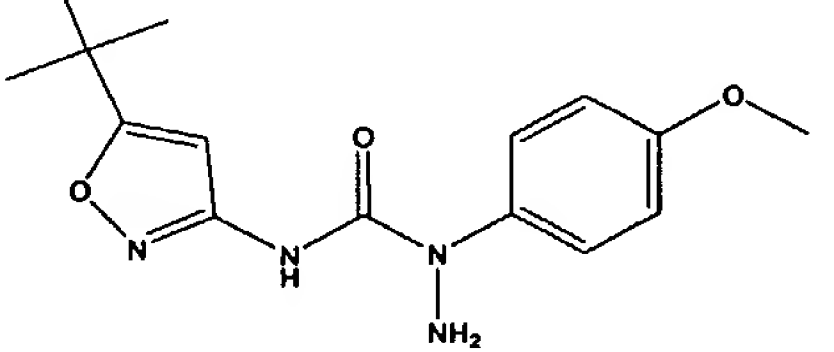
15

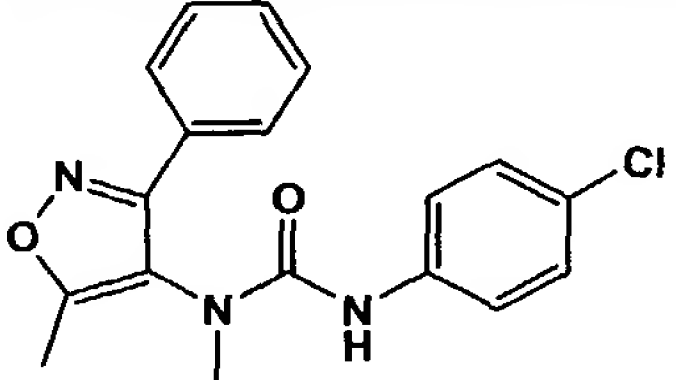
A solution of 5-tert-butylisoxazole-3-isocyanate (166 mg, 1 mmol) in 0.5 ml dimethylacetamide was added to a solution of 4-methoxy-N-methylaniline in 0.5 ml

dimethylacetamide (137 mg, 1 mmol), and the mixture was heated at 80°C overnight. After cooling to room temperature, 20 ml water was added and the mixture was extracted with 3x30 ml EtOAc. The combined organic phases were washed with brine, dried over magnesium sulfate, and evaporated. Purification of the product, N-(methyl)(4-methoxyphenyl)-N-(5-t-butyl-3-isoxazolyl) urea, was accomplished by flash chromatography (silica gel, hexanes, 0-50% EtOAc).

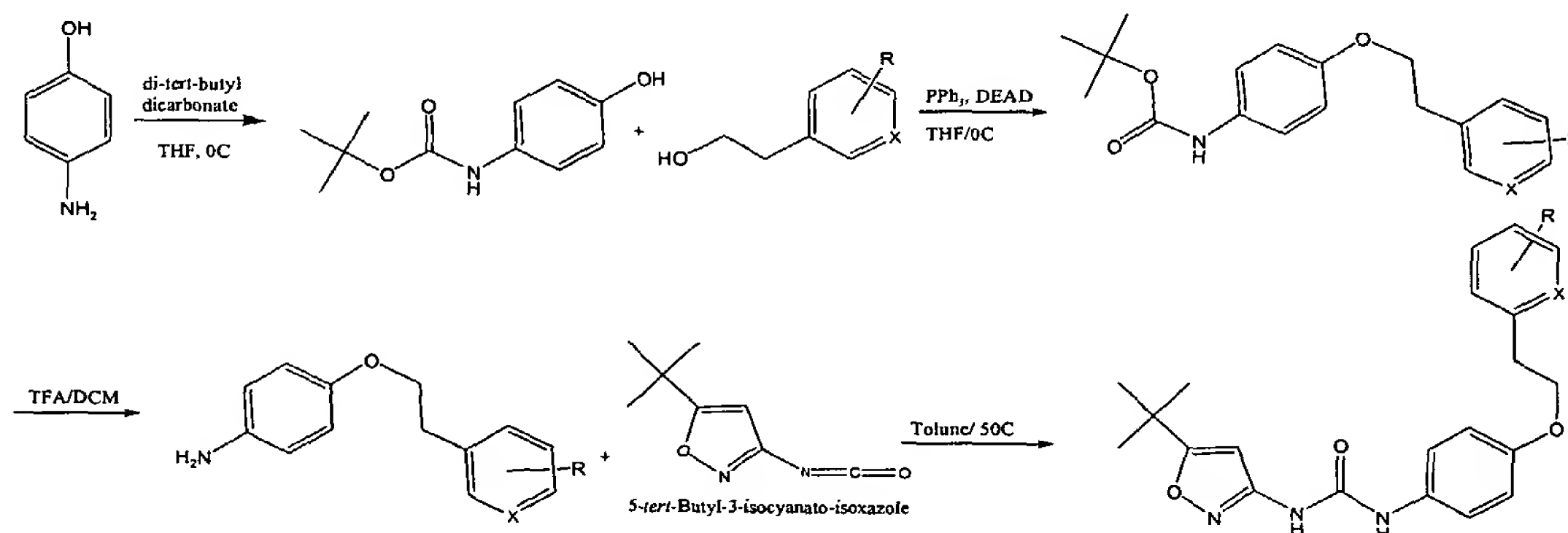
Compounds J2 through J15 were synthesized in a manner analogous to Compound J1 using similar starting materials and reagents. The structures are shown below in Table J:

Table J

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
J1		J2	
J3		J4	
J5		J6	
J7		J8	
J9		J10	
J11		J12	
J13		J14	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
J15			

Example K: Synthesis of Compounds with ether-alkyl chains



The following general procedure was used to synthesize compounds having the ethylene, propylene, or butylenes linkers. To a stirring solution of 4-aminophenol (1eq) in THF at 0°C, di-tert-butyl dicarbonate (1eq) in THF was slowly added dropwise over 30 minutes. The reaction was stirred at 0°C and allowed to warm to room temperature overnight. The solvent removed and diluted with ethyl acetate. It was then extracted with water three times, and the organic layer was dried over magnesium sulfate. The solid was recrystallized from dichloromethane.

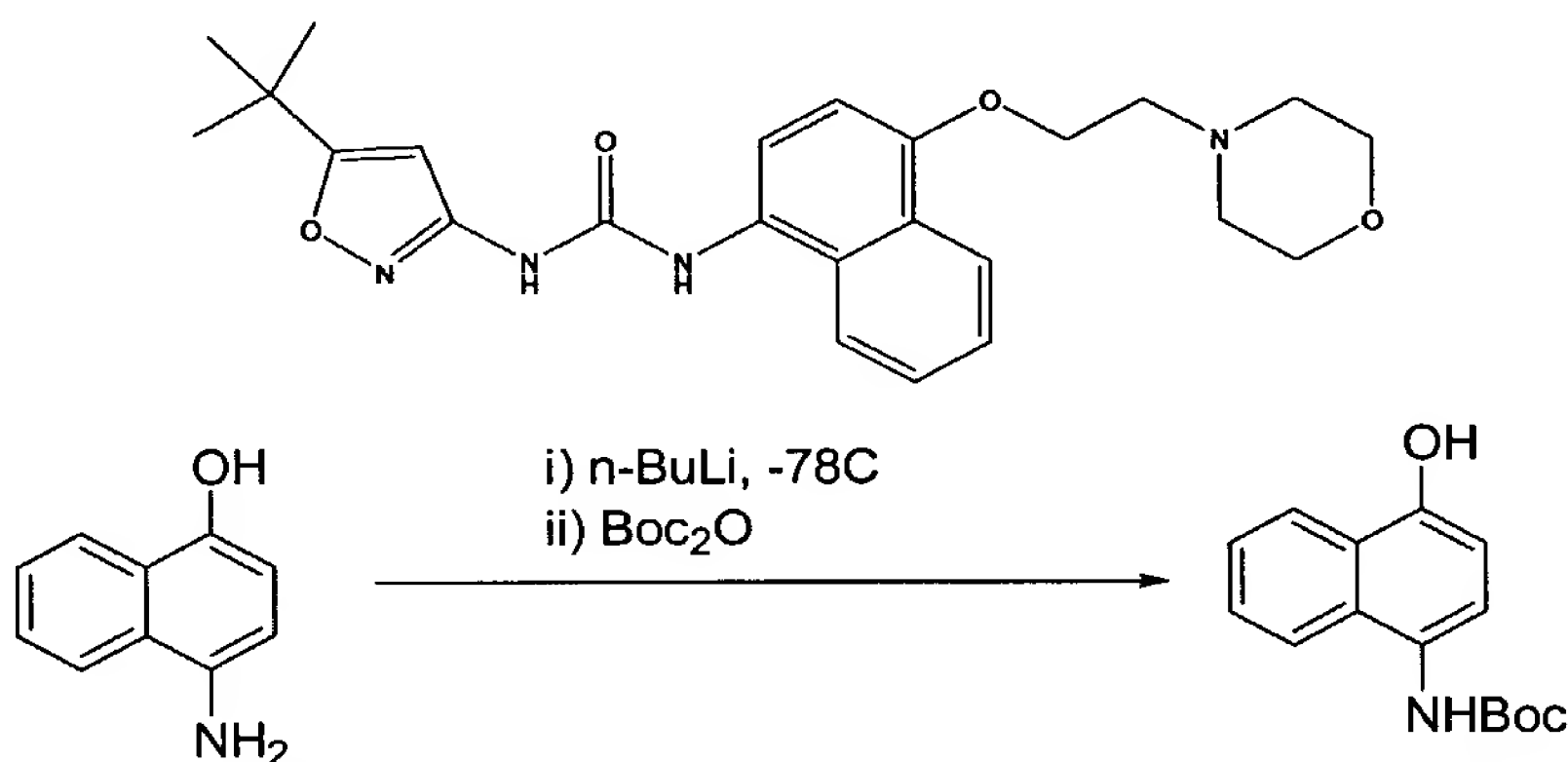
In a dry flask flushed with nitrogen gas bocaminophenol (1eq), substituted alcohol (1eq) and triphenylphosphine (1.5eq) was added and then dissolved with THF. The flask was cooled to 0°C and diethyl azodicarboxylate (1.5eq) was added dropwise. The reaction stirred overnight at room temperature. THF was removed under vacuum and the mixture was purified by HPLC.

The protected substituted ethoxyaniline was dissolved in dichloromethane and trifluoroacetic acid was added. The reaction stirred at room temperature for 1 hour. The excess trifluoroacetic acid was removed in vivo.

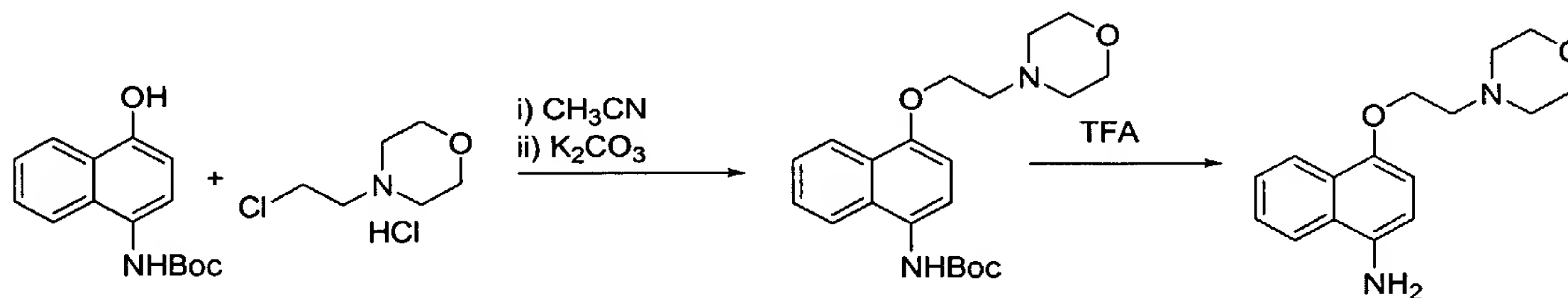
The substituted ethoxyaniline (1eq) was mixed with 5-tert-Butyl-3-isocyanato-

isoxazole (1eq) and dissolved in dry toluene. The reaction stirred at 50°C overnight. The solvent was removed and purified by HPLC. Compound W, compound X, and others in the series were synthesized using the procedure described above.

Synthesis of Compound K1: 1-(4-(2-morpholinoethoxy)naphthyl)-3-(3-tert-butylisoxazol-5-yl)urea

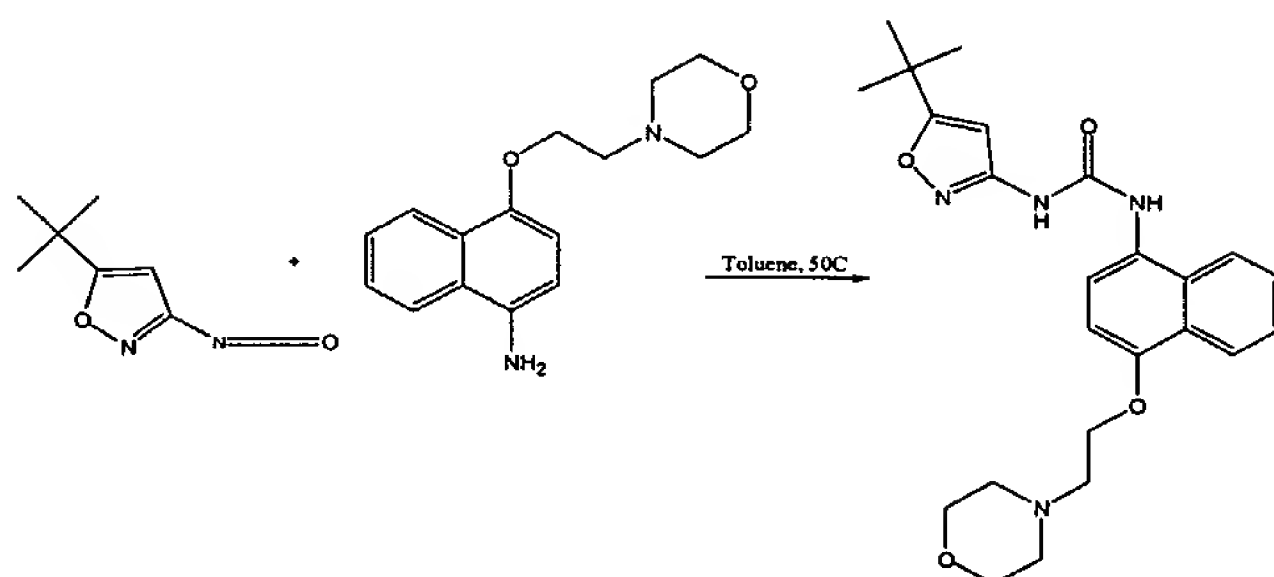


To a mixture of 4-amino-1-naphthol hydrochloride (15g) in 100mL dry THF at -78 C was added dropwise over 1h n-BuLi (43 mL of a 1.6M solution in hexanes). After the addition was complete the mixture was allowed to warm to room temperature and then cooled to -78 C and di-tert-butyl dicarbonate (Boc₂O) (16.5g in 100mL THF was added over a period of 20 min). The mixture was slowly warmed to room temperature and stirred for 24 h and then most of the volatiles removed in vacuo. The residue was diluted with ethyl acetate and washed with water (3 x 100 mL) and brine (100 mL) and filtered through celite and dried over magnesium sulphate. Column chromatography (30% EtOAc/hexanes) gave 20g of pure product.



To a solution of (4-Hydroxy-naphthalen-1-yl)-carbamic acid tert-butyl ester (3g) and 4-(2-Chloro-ethyl)-morpholine hydrochloride (2.22g) in 25mL of acetonitrile was added powdered potassium carbonate (6g) and the solution heated overnight at 80 C. It was cooled,, diluted with EtOAc and water. The organic layer was washed with water, brine and dried over anhydrous magnesium sulfate and the volatiles removed in vacuo. Purification by silica gel

chromatography (10% EtOAc/hexanes) gave 2.3 g of pure product.



To a flask 5-tert-Butyl-3-isocyanato-isoxazole (242mg, 1eq) and substituted aniline (159mg, 1eq) was added and dissolved in toluene. The reaction was allowed to stir at 50°C for three hours. The solvent removed and the mixture was purified by HPLC. Yield: 188mg (47%)

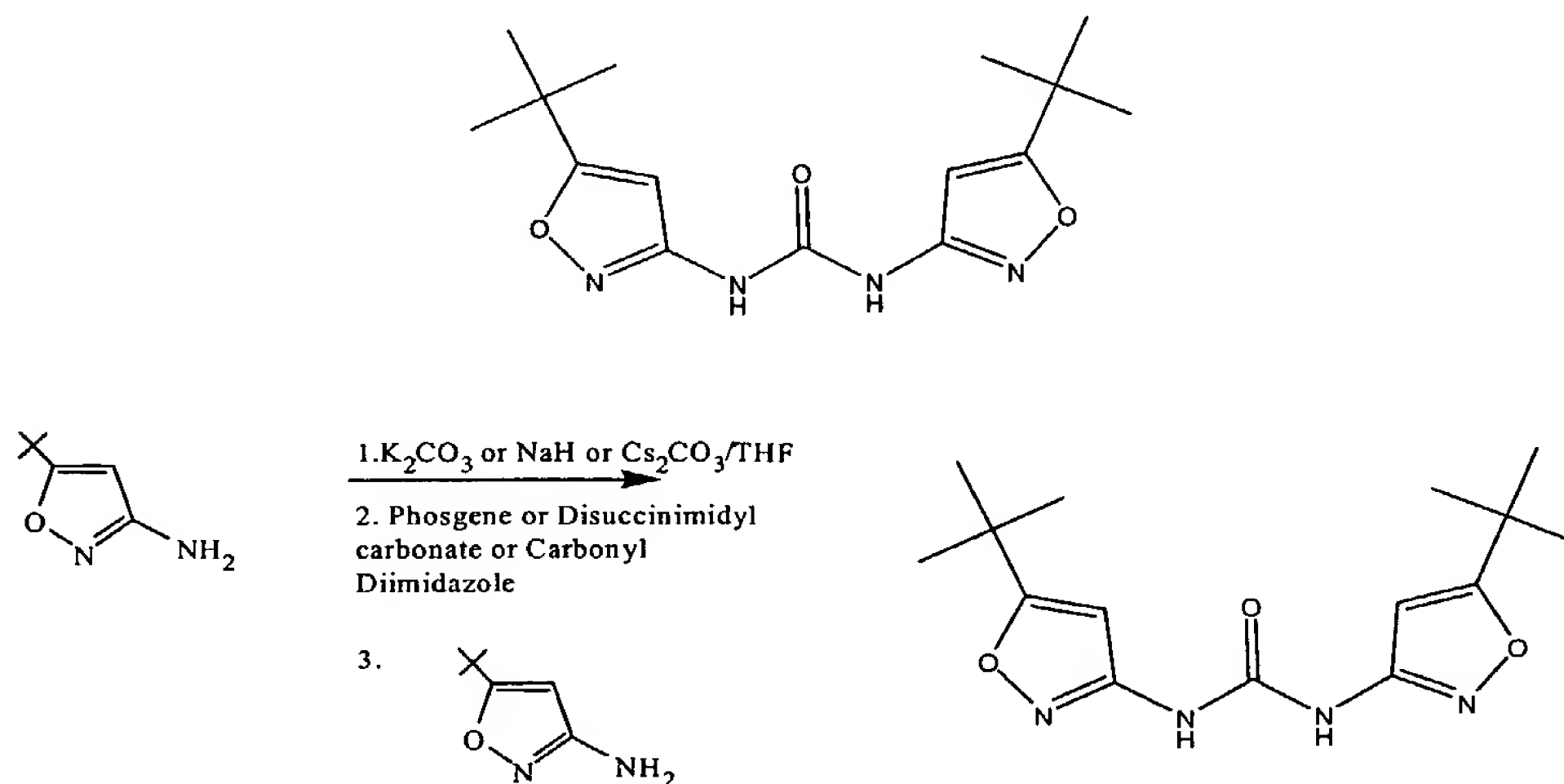
Compound K2 was synthesized in a manner analogous to Compound K1 using similar starting materials and reagents. The structures are shown below in Table K:

Table K

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
K1		K2	

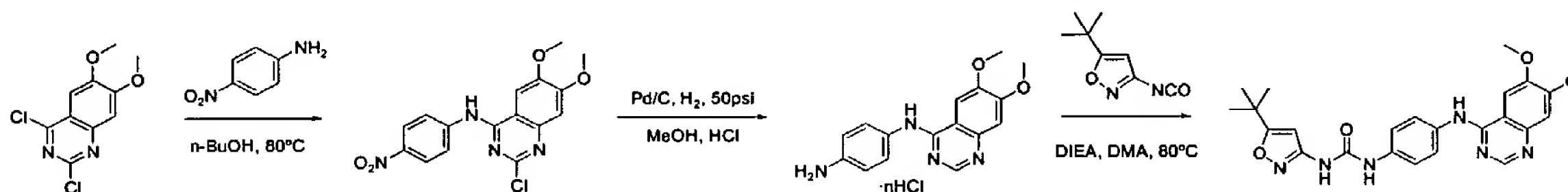
Example L: Exemplary Synthesis of Isoxazole-Urea

Synthesis of Compound L1: 1,3-bis(5-tert-butylisoxazol-3-yl)urea

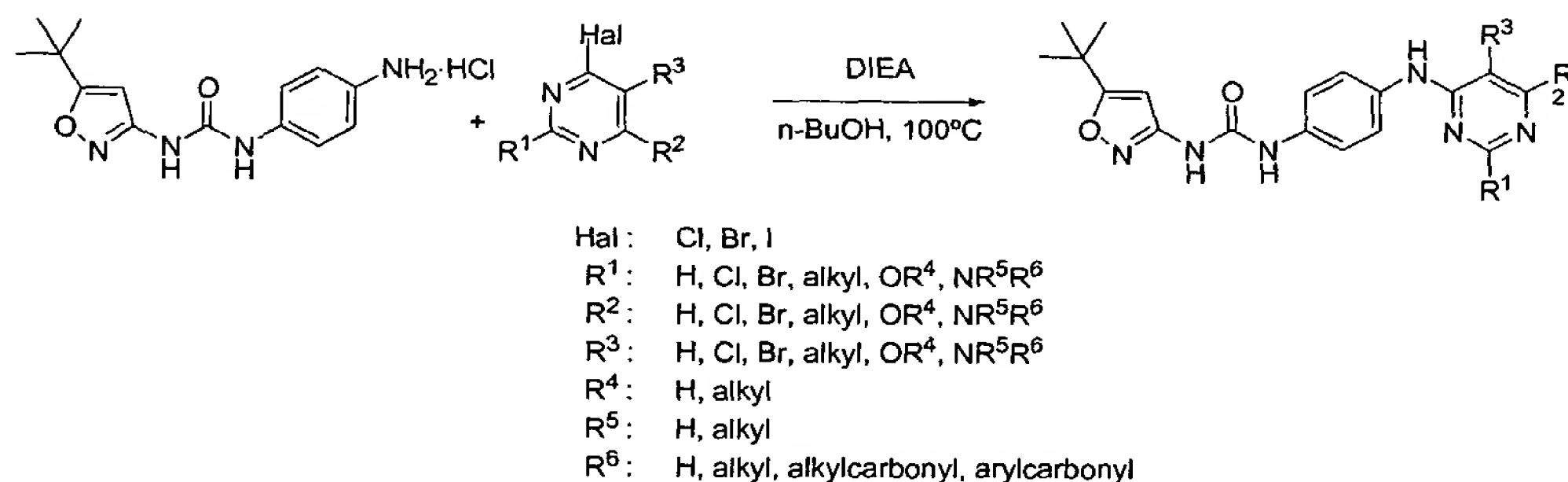
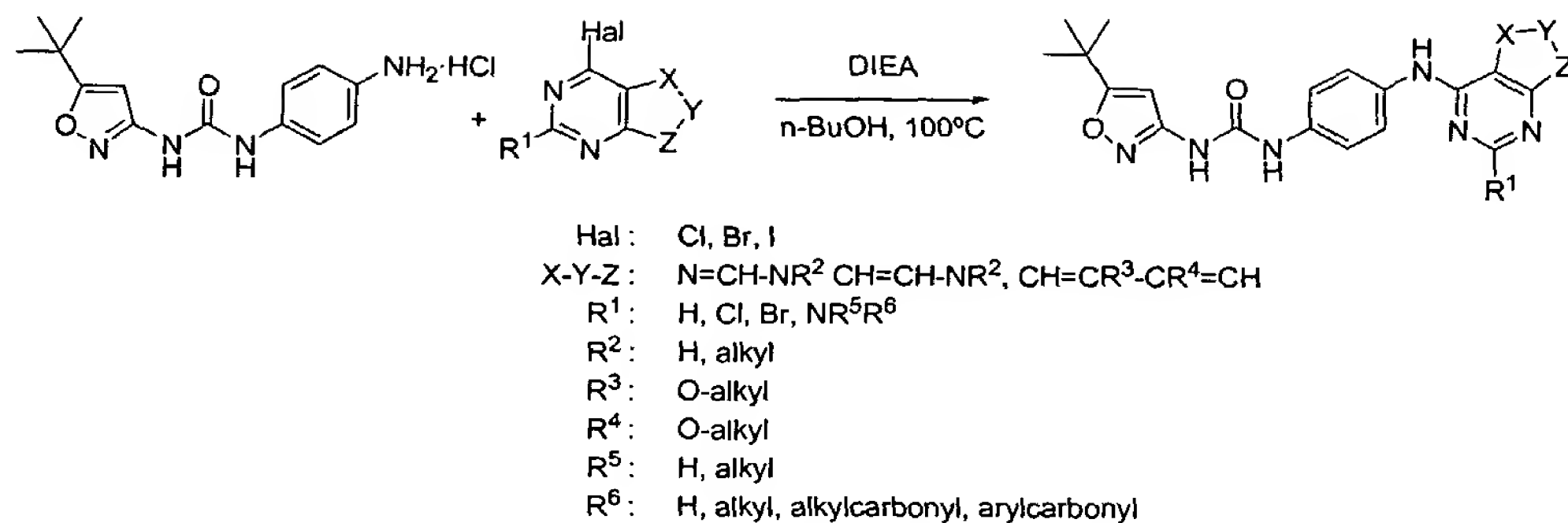


A mixture of amine 5-tert-butyl-isoxazol-3-ylamine (1 eq) in dry THF is stirred at room temperature under argon for an hour. Then the stirred suspension is cooled to 0°C and to it is added dropwise a solution of phosgene or disuccinimidyl carbonate or carbonyl diimidazole (1.2 eq). The reaction is stirred at 0°C for half an hour. Then 5-tert-butyl-isoxazol-3-ylamine in THF is added dropwise and the reaction is allowed to warm to room temperature and stirred overnight. The solvent is removed and extracted with ethyl acetate and water. The organic layer is dried over magnesium sulfate and solvent removed, and the 1,3-bis(5-tert-butylisoxazol-3-yl)urea product purified by HPLC.

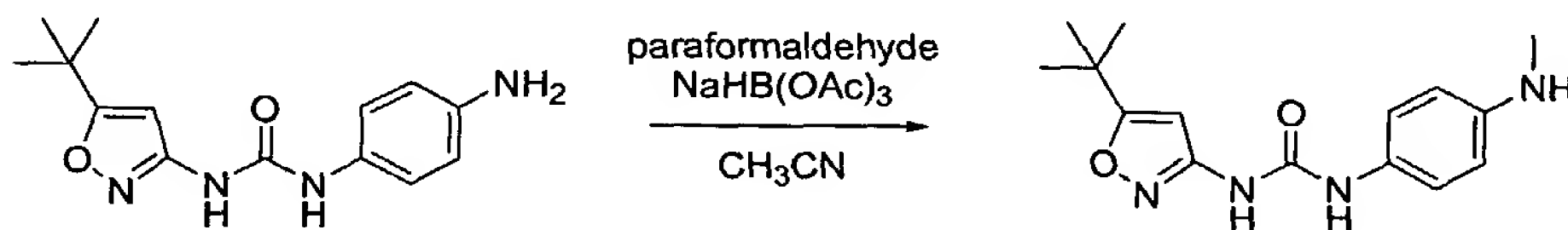
Example M: Exemplary Synthesis of Pyrimidine Containing Compounds



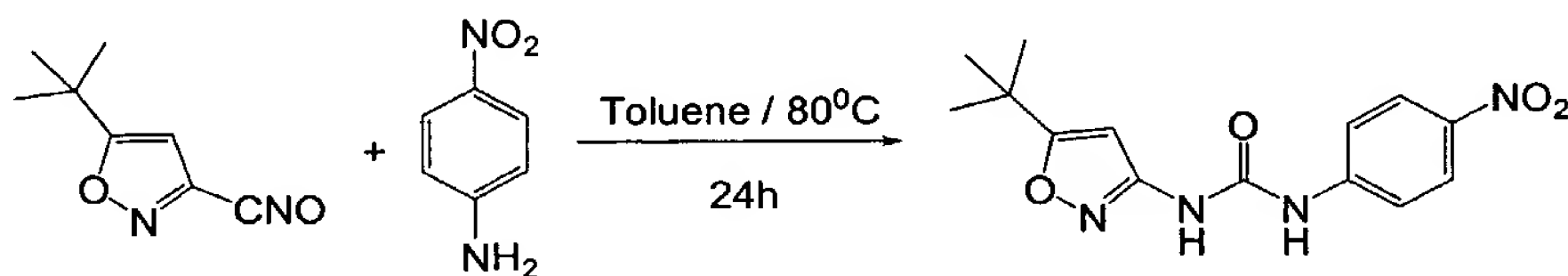
Dichloro-dimethoxyquinazoline was heated for 3 hours at 80°C with one equivalent p-nitroaniline in n-butanol. After cooling to room temperature, isopropanol was added and the insoluble product was collected by filtration. Reduction was accomplished using 10%Pd/C in methanol at 50psi in the presence of hydrochloric acid. The resulting aniline was reacted with the oxazole isocyanate in DMA at 80°C in the presence of DIEA. The urea product was purified by HPLC.



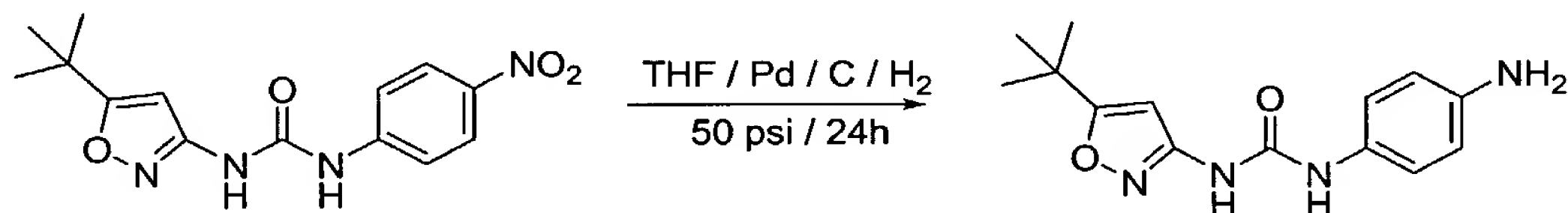
A mixture of aminourea hydrochloride (155mg, 0.5mmol), halopurine/haloquinazoline/halopyrimidine (0.5 mmol), and DIEA (90μl, 0.5mmol) in *n*-butanol (2-5ml) was heated at 100°C for 1-16h. The product was purified by HPLC.



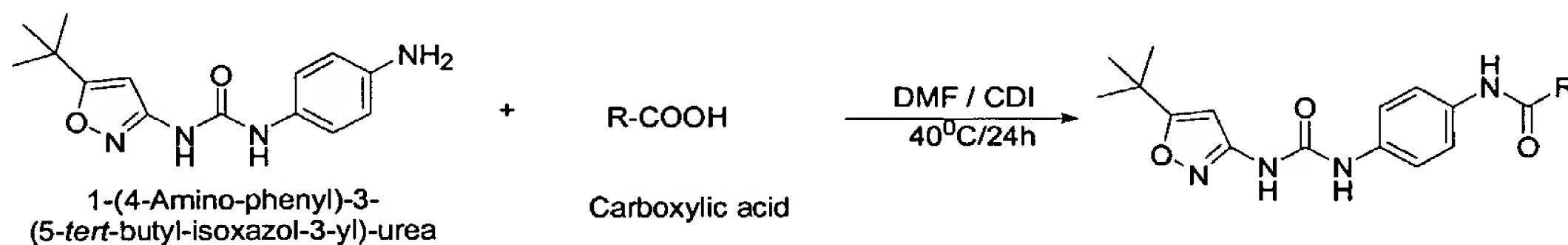
A mixture of aminourea (274mg, 1mmol), paraformaldehyde (30mg, 0.33mmol), sodium triacetoxyborohydride (636mg, 3mmol) and 10 drops glacial acetic acid was stirred at room temperature over night. The solvent was evaporated completely and the residue was treated with sat. aq. NaHCO₃. The solids were collected by filtration and purified via HPLC. The resulting methylaniline was used in amide formations and aryl aminations as described above.

Example N: Exemplary Synthesis of Compounds Containing Amide Linkers

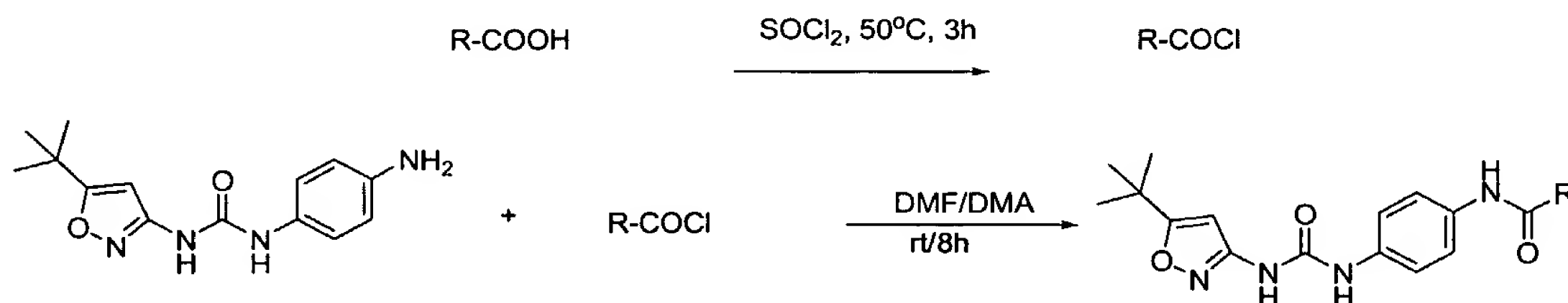
1 gm. (6 mmol) of 5-tert-butyl-isoxazole-3-isocyanate and 0.83gm (6 mmol) 4-nitro-phenylamine were dissolved in 20ml dry toluene and stirred at 80°C for 24h. The resulting suspension was cooled to room temperature and filtered off to give the title compound as a yellow solid. The product was used in the next step without further purification. Yield: 1.7 g (92%), LC/MS [MH⁺] 305.



1.5 gm of 1-(5-tert-butyl-isoxazol-3-yl)-3-(4-nitro-phenyl)-urea was dissolved in 50ml THF and 0.1 g of 10% Pd/C was added. The solution was stirred under hydrogen at 50 psi. for 24h than filtered trough Celite pad. The organic solvent was evaporated under vacuum and the resulting residue was triturated with ethyl acetate. Yield: 1.3g (96%), LC/MS [MH⁺] 275.



1 equivalent of the carboxylic acid and 1.1 equivalent of CDI were dissolved in dry DMF and stirred at 40°C for 2 h, than 1 equivalent of aniline was added. The reaction mixture was stirred at 40°C overnight and the final product was purified by preparative HPLC.



Alternatively, 1 equivalent of the carboxylic acid and 1.1 equivalent of thionyl chloride were heated in a sealed tube at 50°C for 3h. The excess thionyl chloride was evaporated, 1 equivalent of aniline in DMF was added, and the solution stirred at room temperature for 8h.

The final product was purified by preparative HPLC.

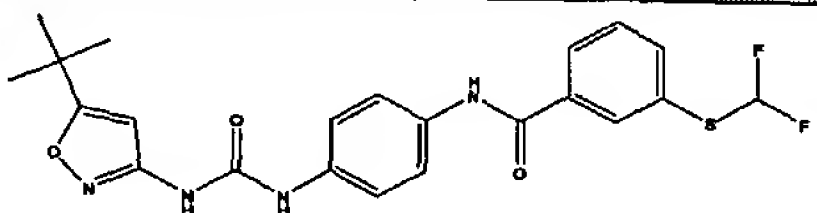
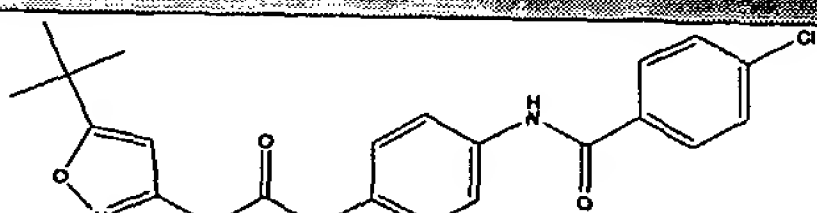
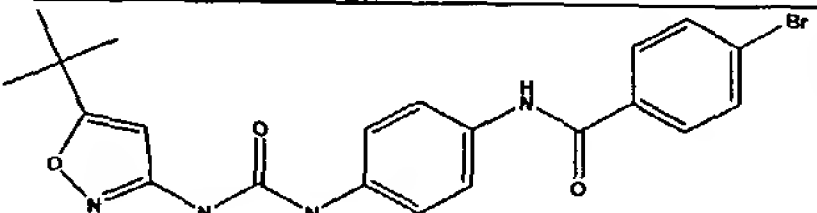
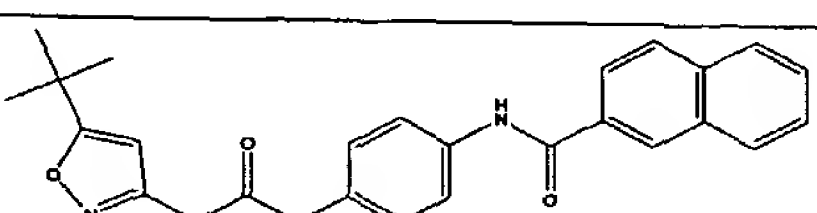
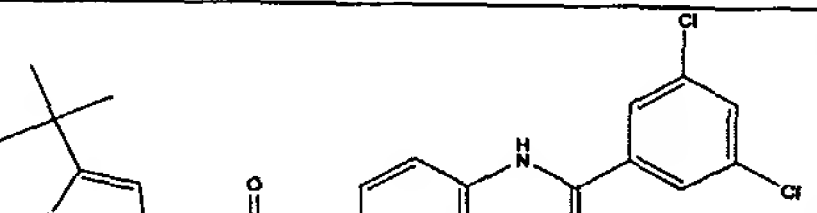
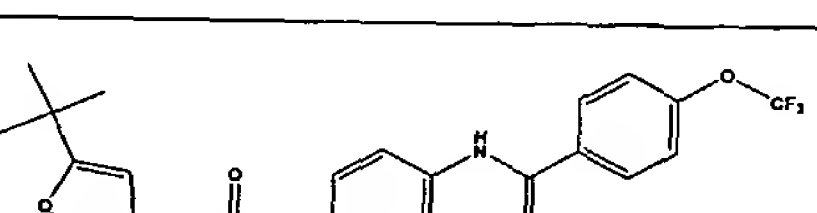
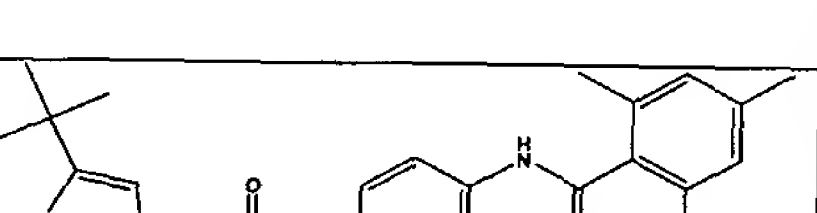
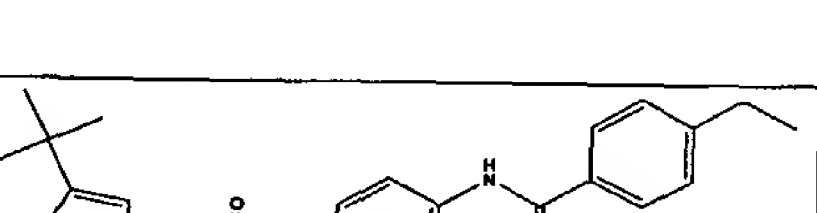

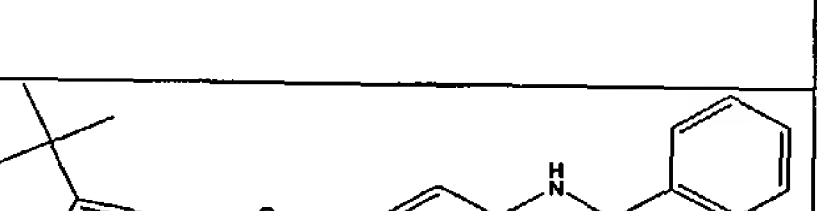
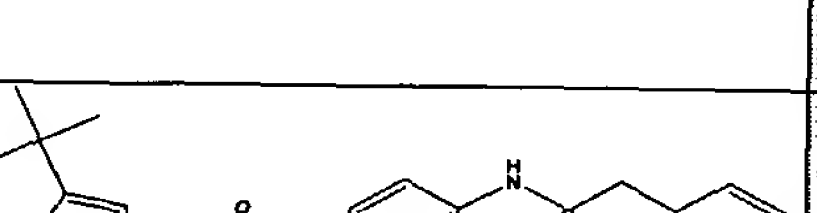
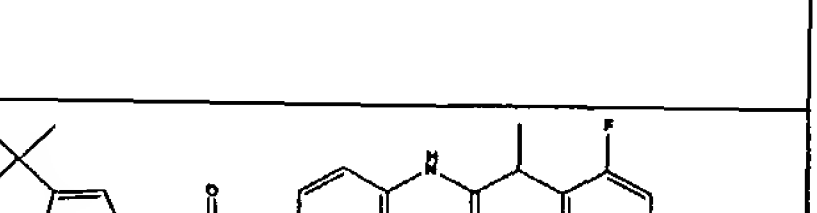
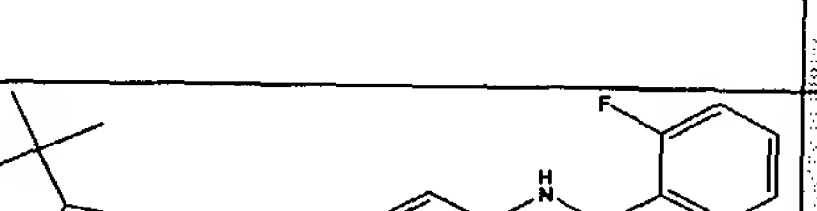
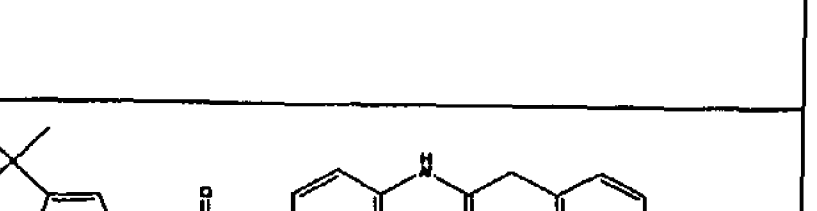
Compounds N1 through N189 were synthesized in a manner analogous to one of the above procedures using similar starting materials and reagents. The structures are shown below in Table N:

5

Table N

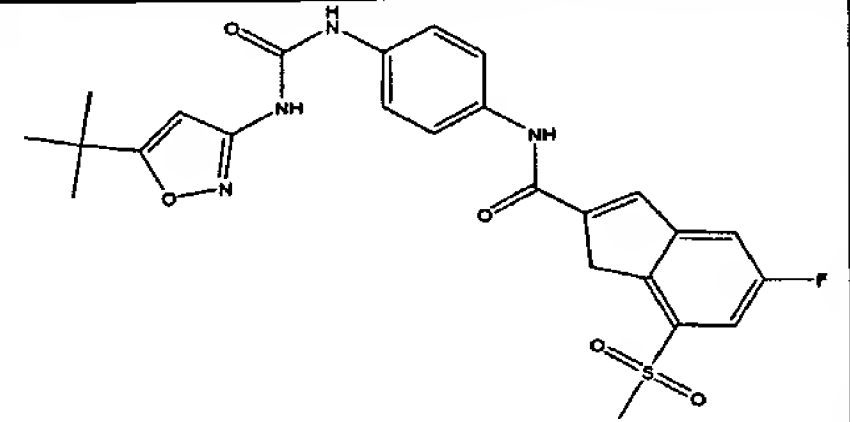
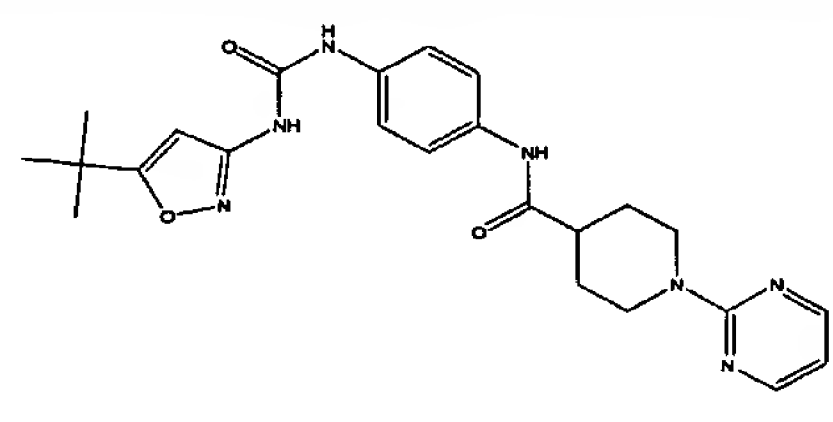
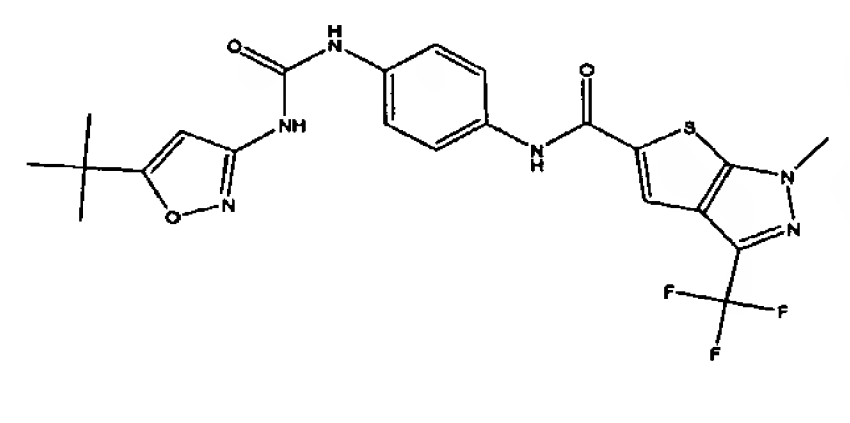
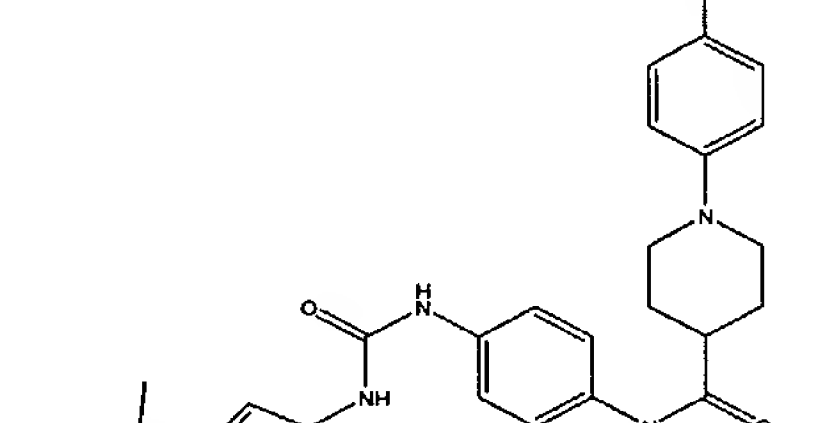
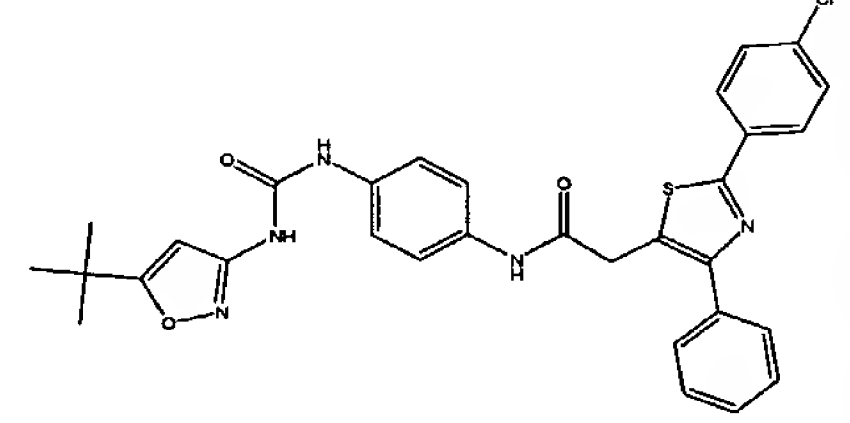
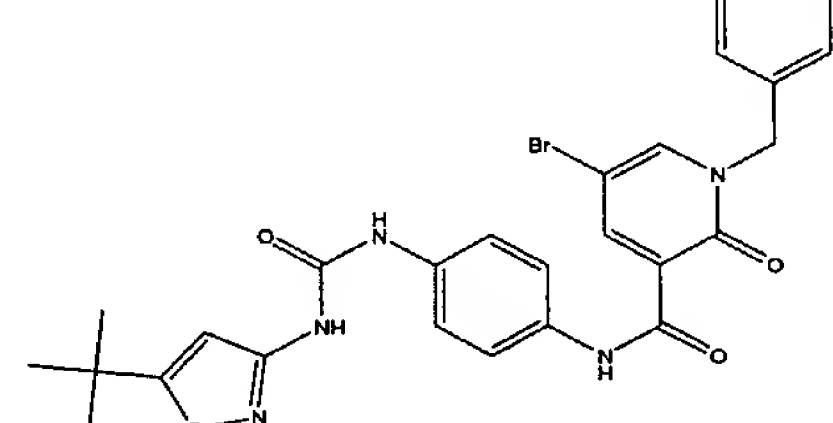
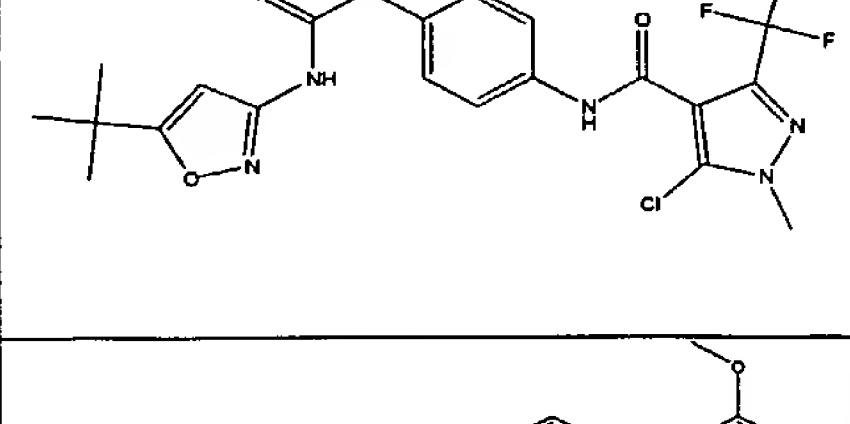
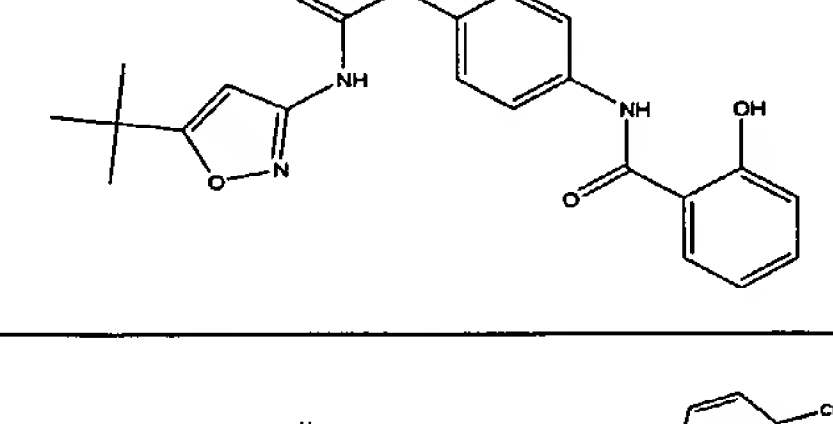
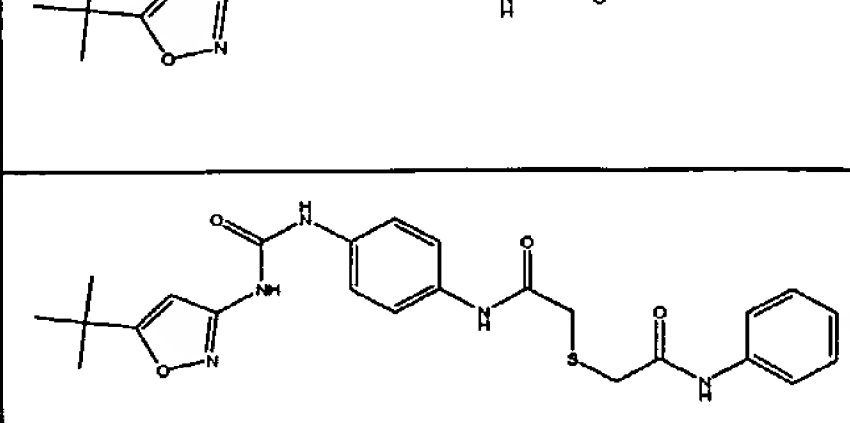
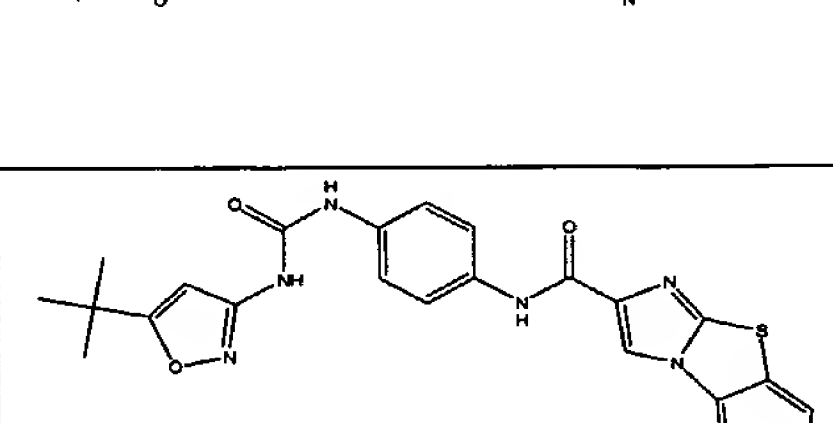


NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
N1		N2	
N3		N4	
N5		N6	
N7		N8	
N9		N10	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N15		N16	
N17		N18	
N19		N20	
N21		N22	
N23		N24	

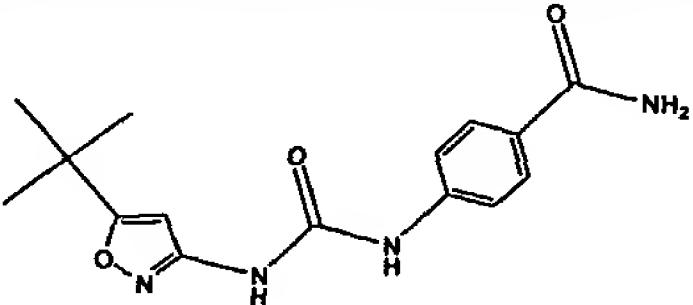
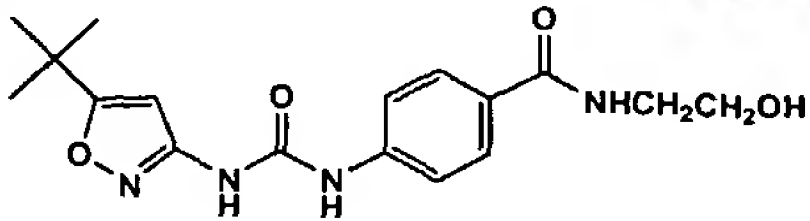
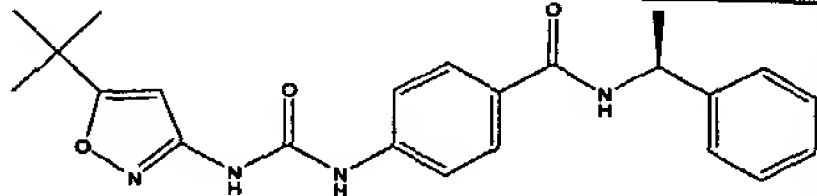
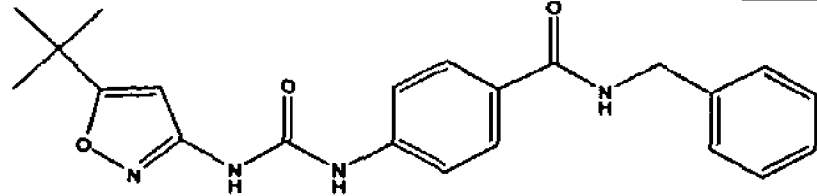
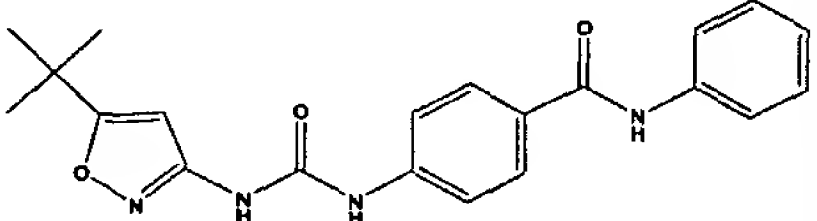
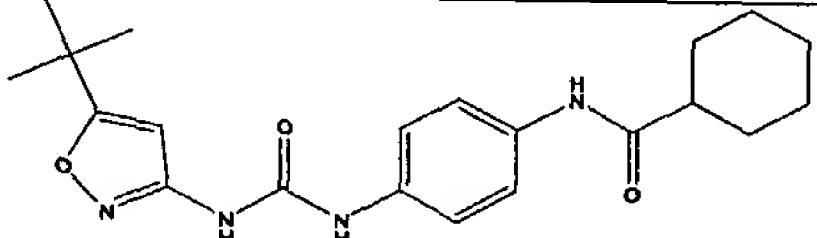
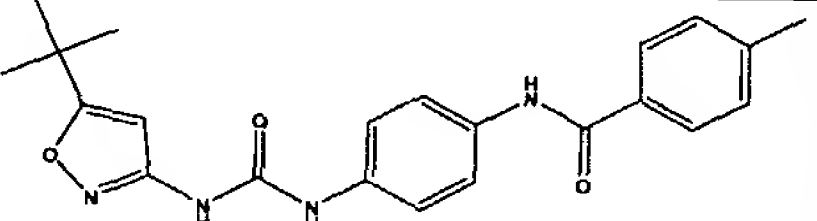
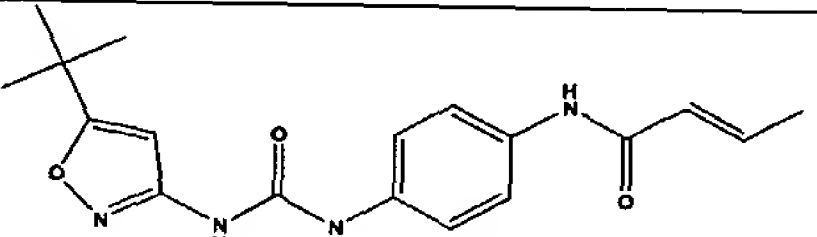
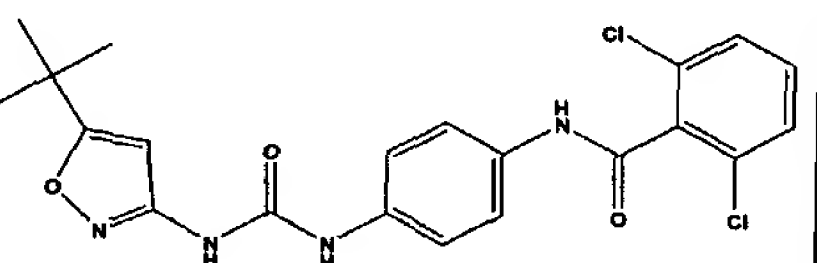
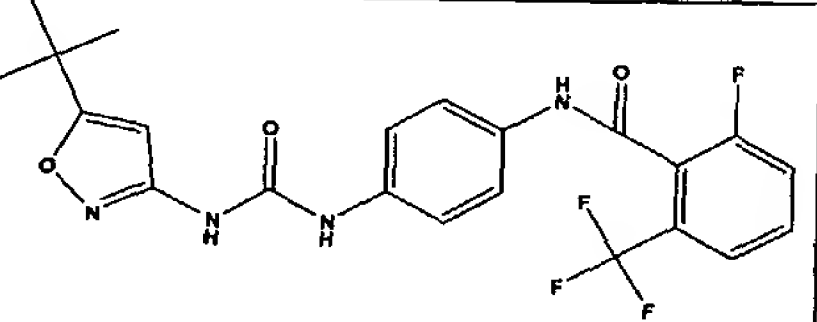
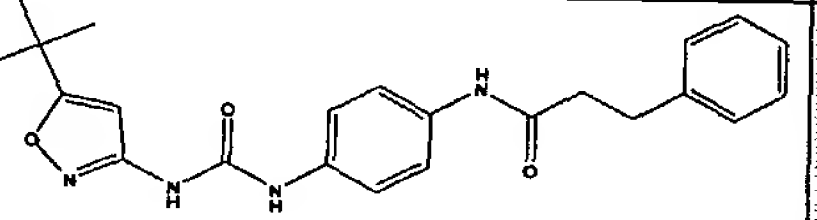
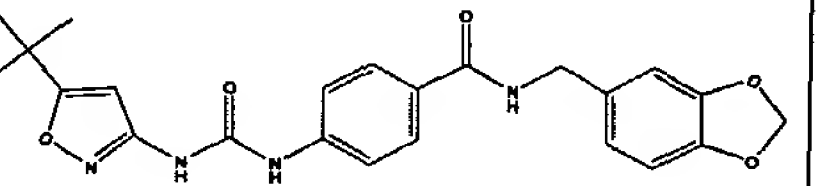
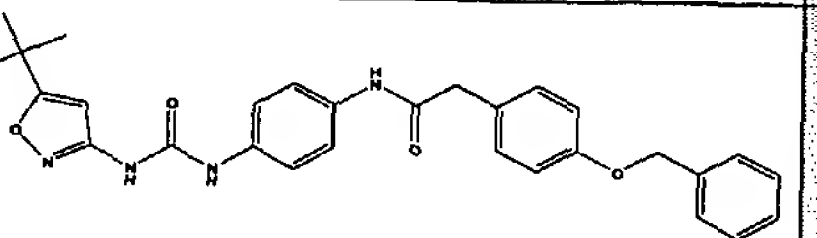
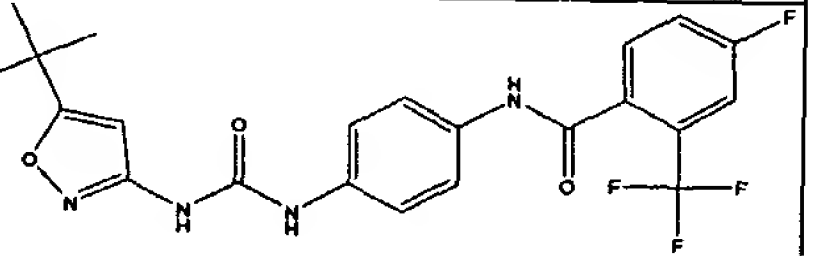
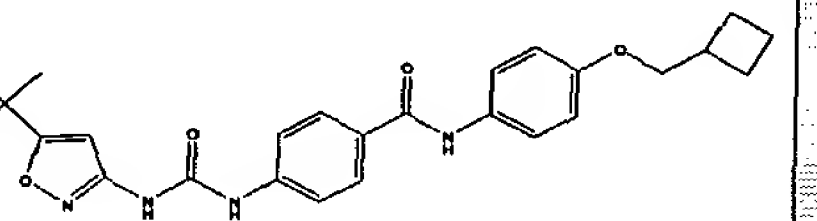
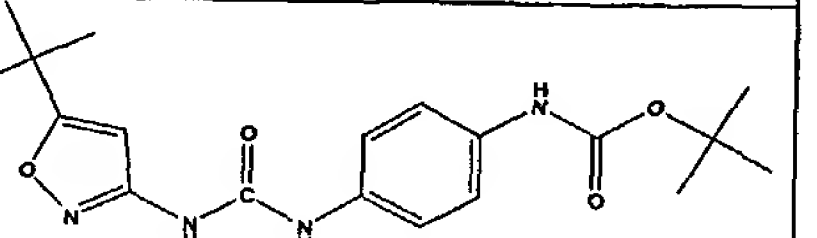
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N27		N28	
N29		N30	
N31		N32	
N33		N34	
N35		N36	
N37		N38	

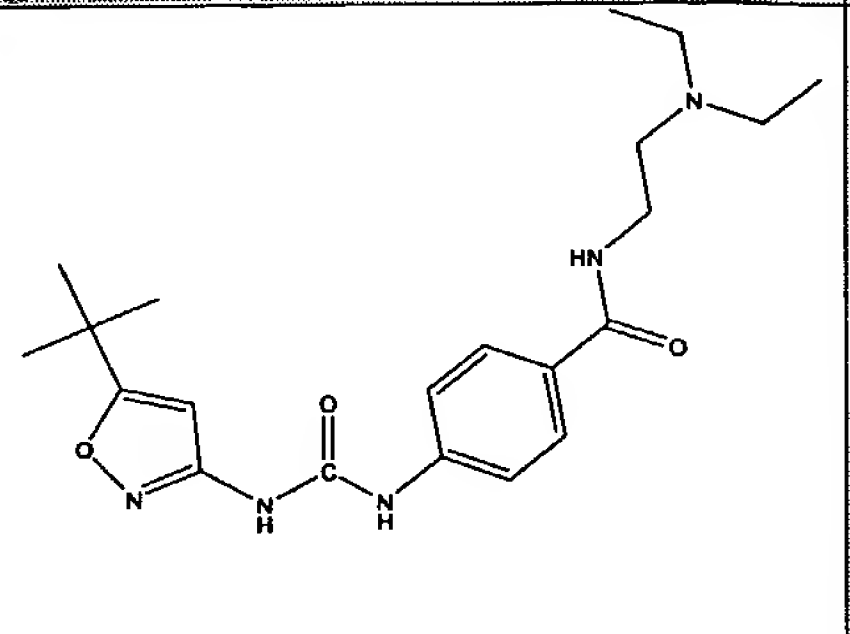
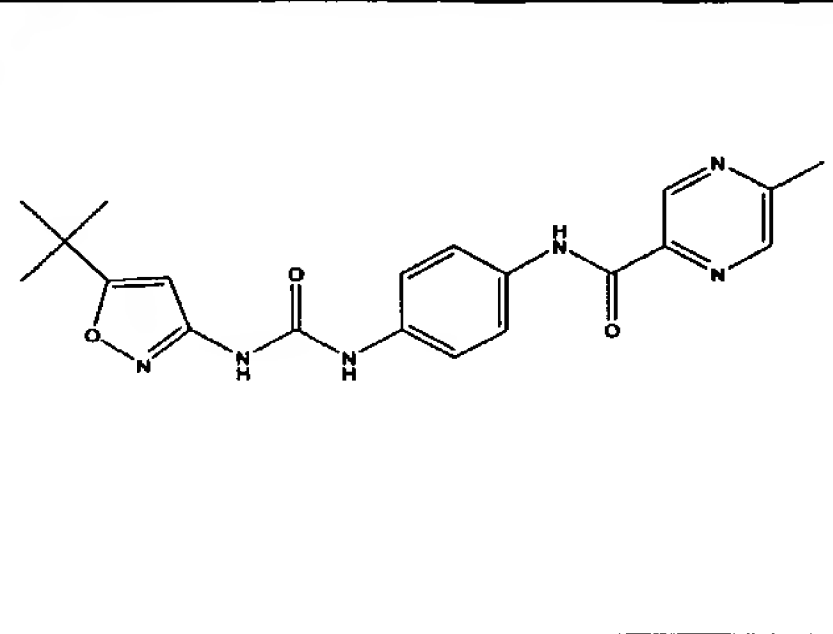
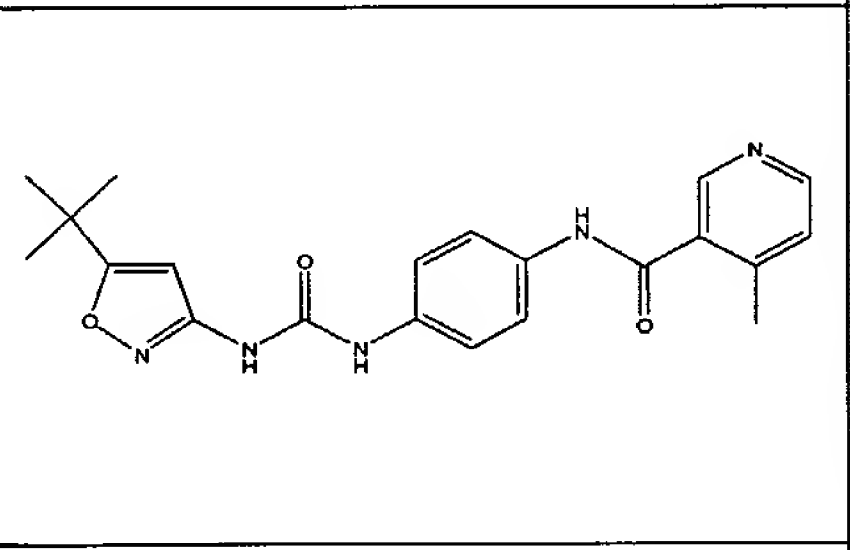
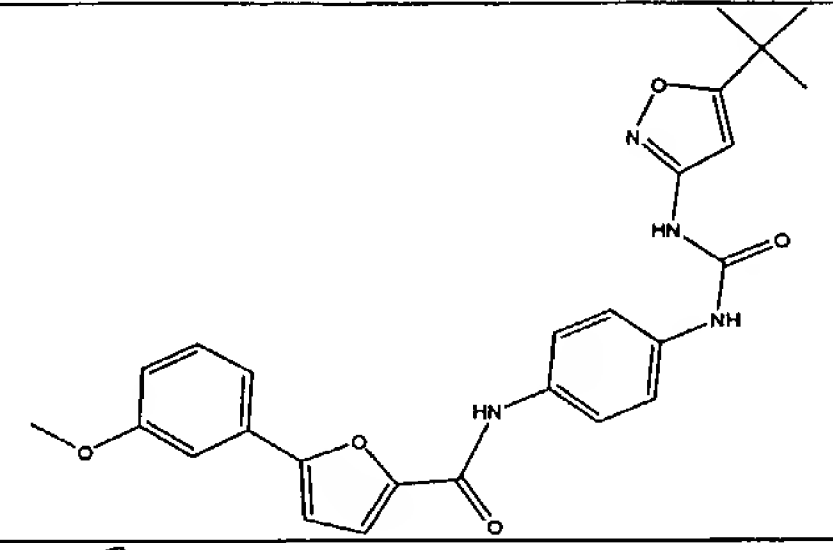
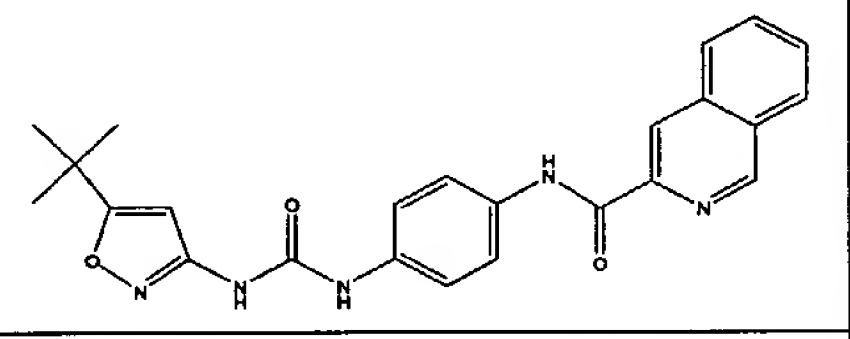
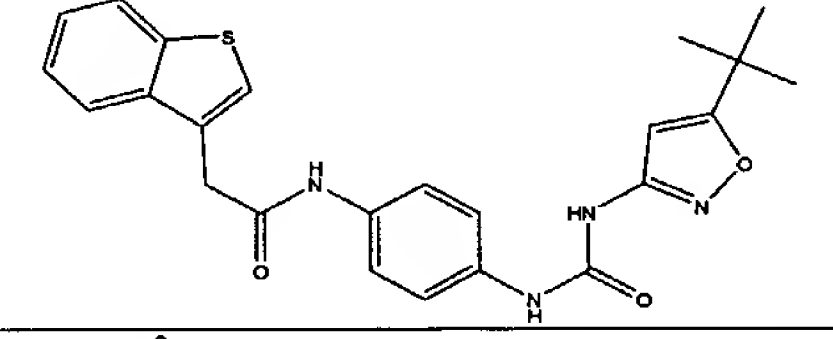
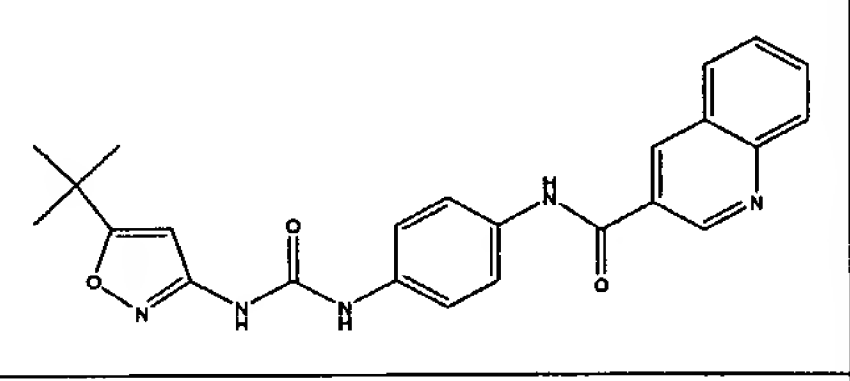
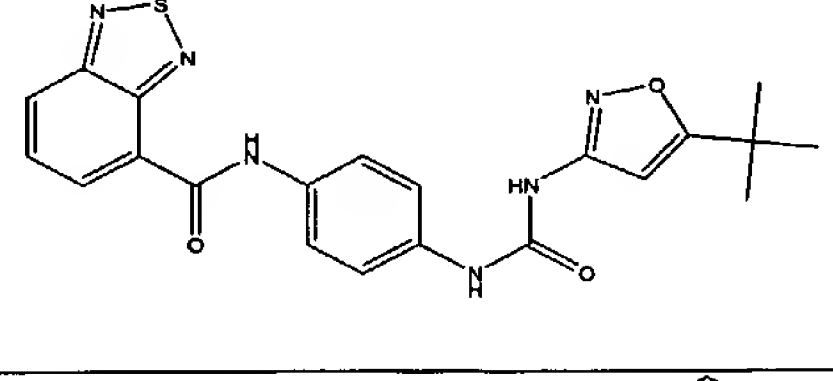
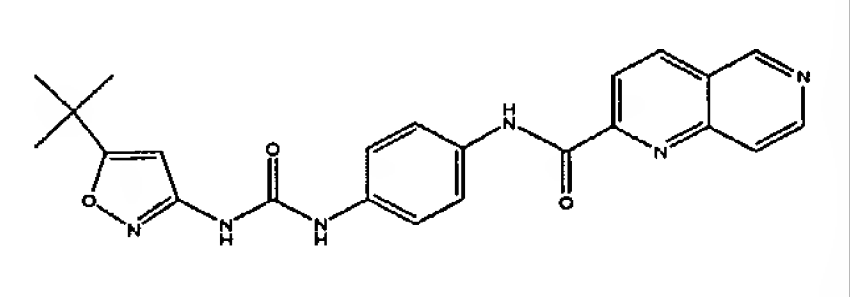
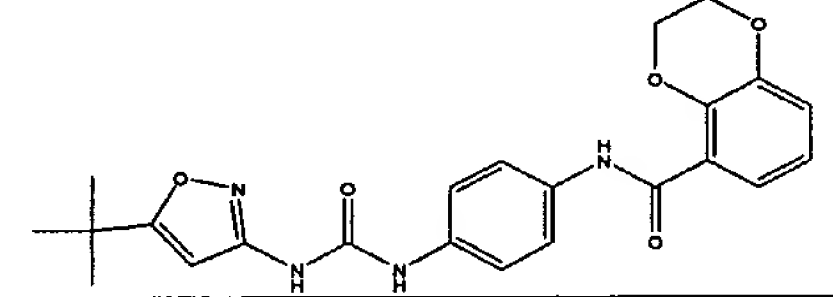
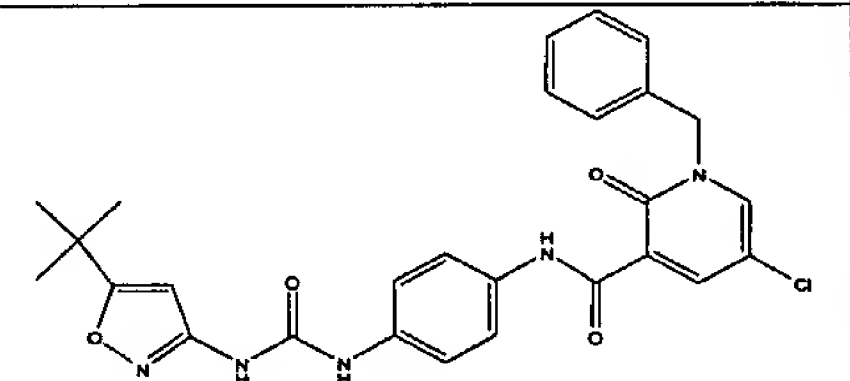
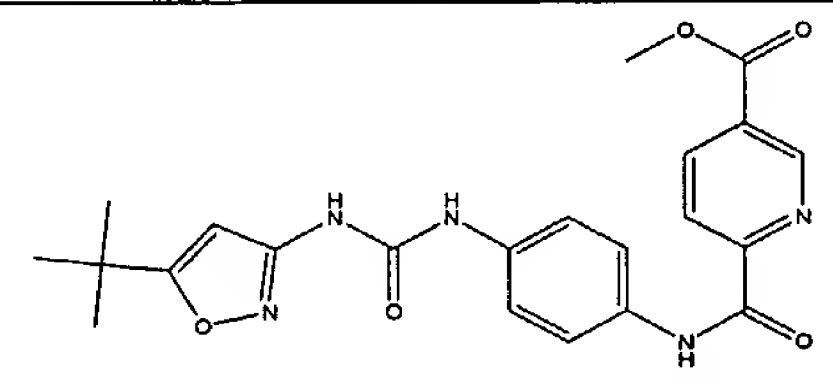
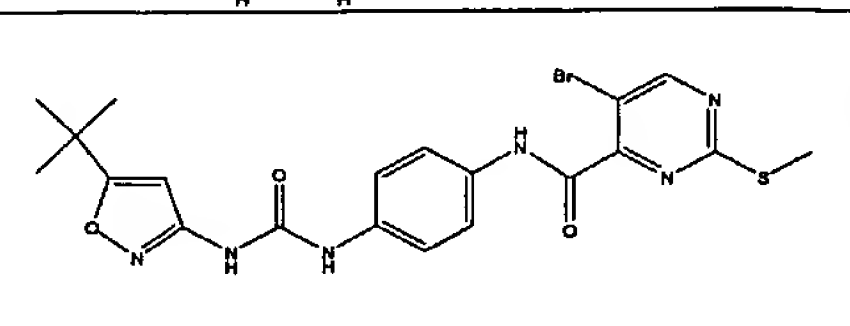
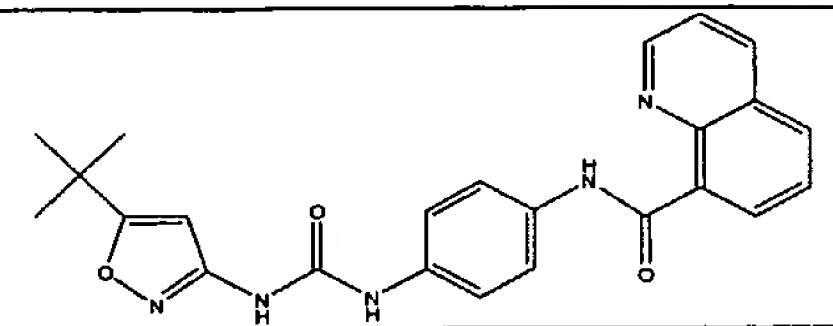
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N41		N42	
N43		N44	
N45		N47	
N48		N49	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N52		N53	
N54		N55	
N56		N57	
N58		N59	
N60		N61	

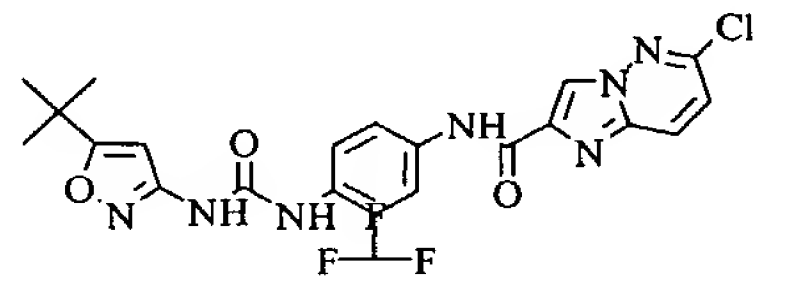
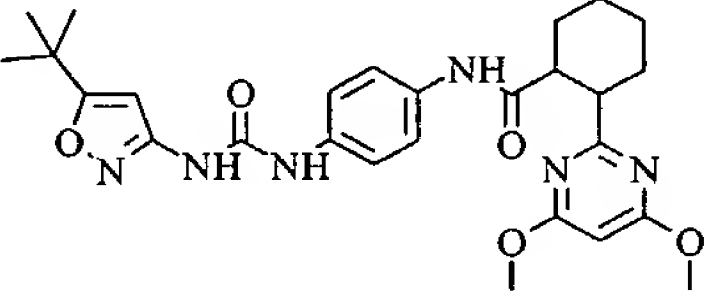
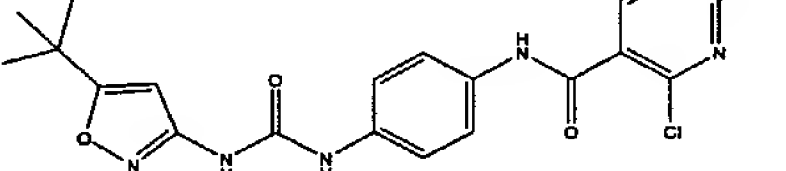
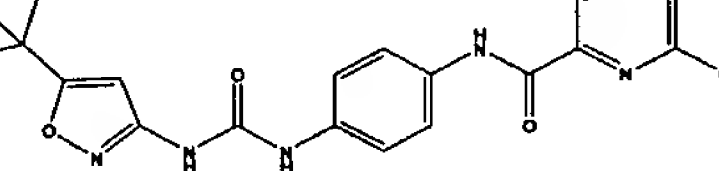
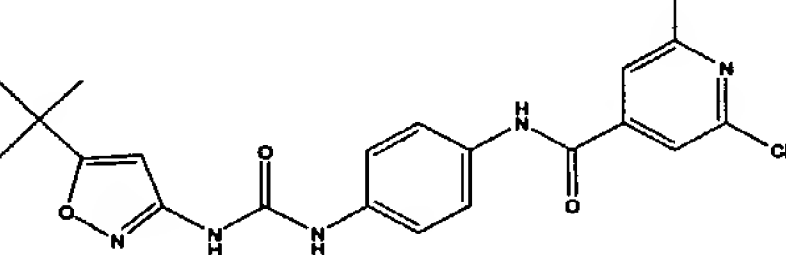
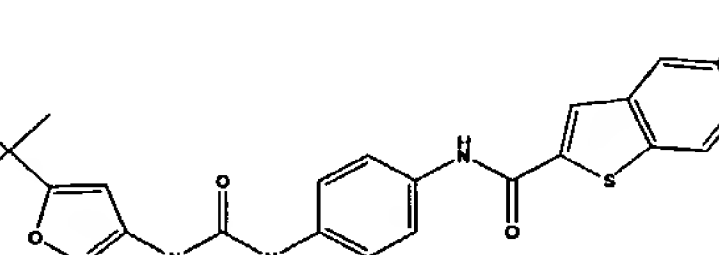
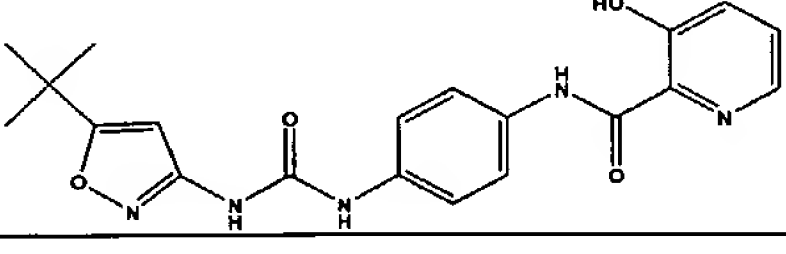
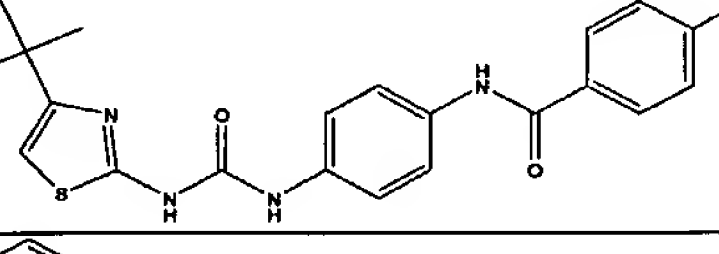
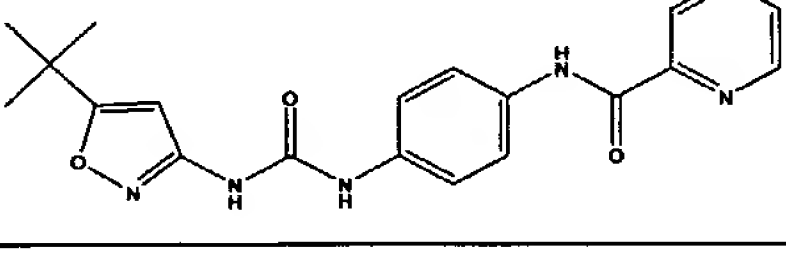
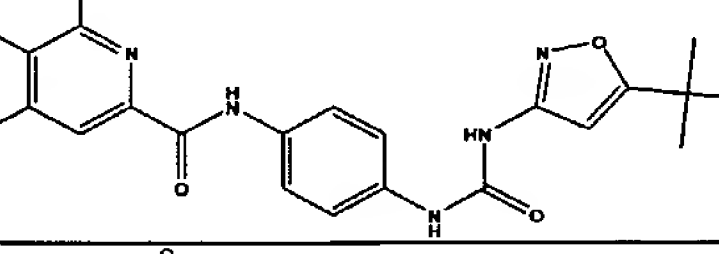
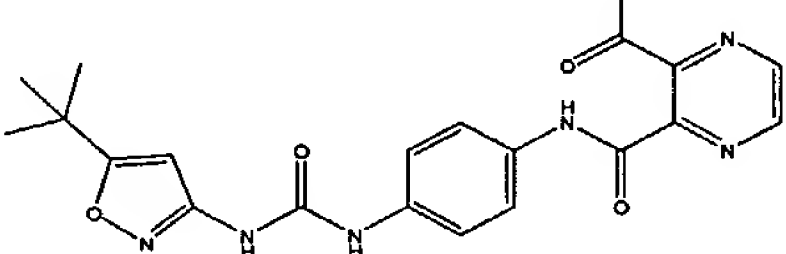
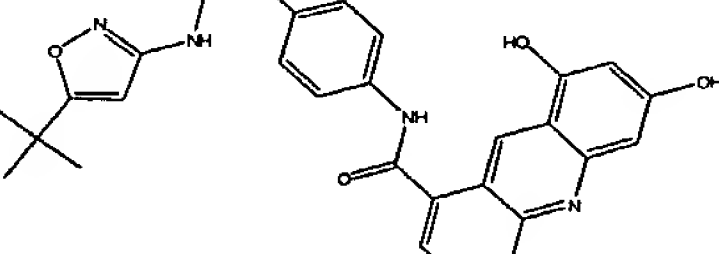
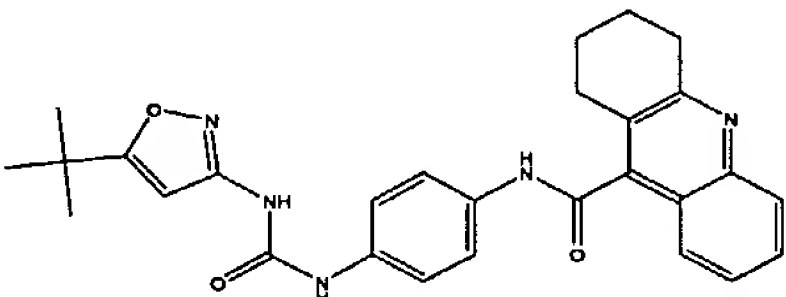
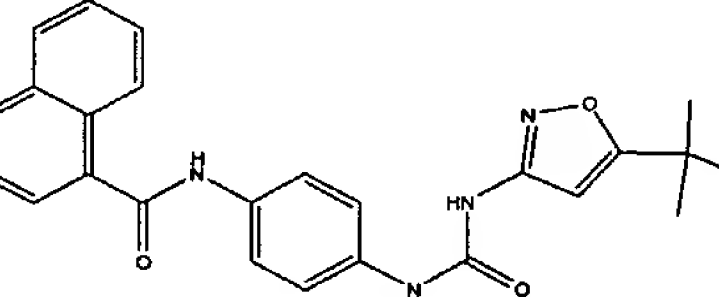
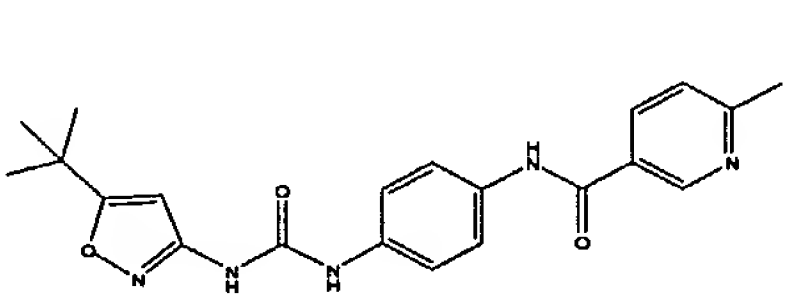
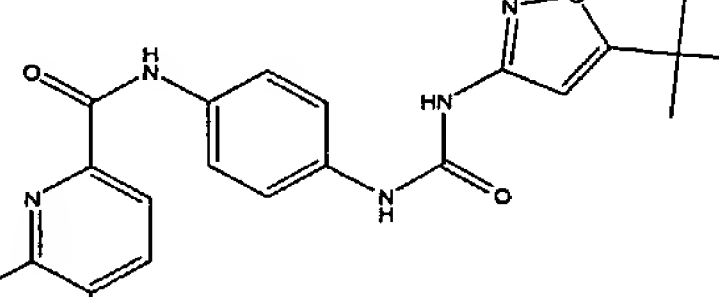
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N64		N65	
N66		N67	
N68		N69	
N70		N71	
N72		N73	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N76		N77	
N78		N79	
N80		N81	
N82		N83	
N84		N85	

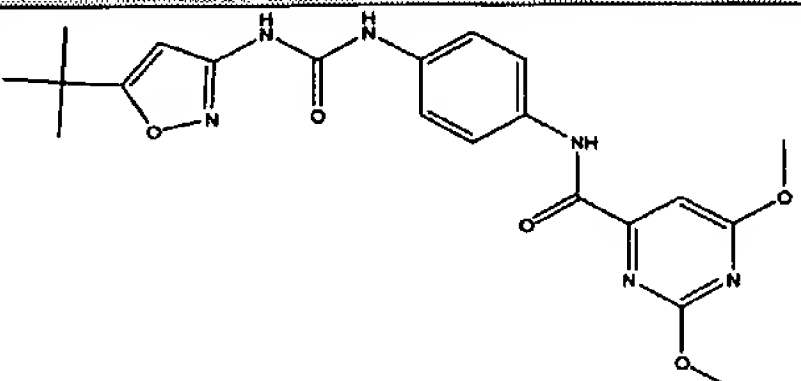
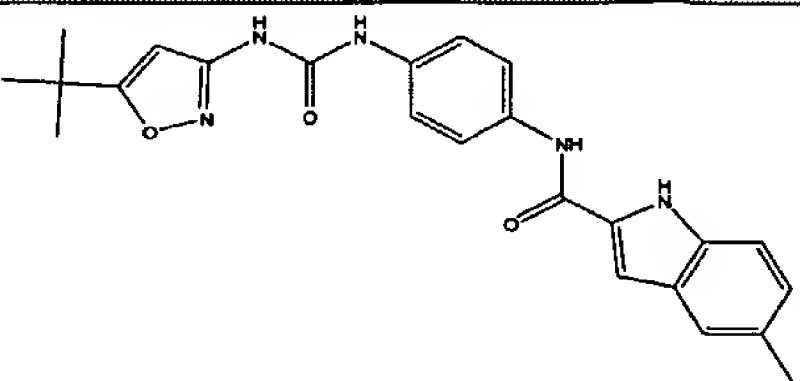
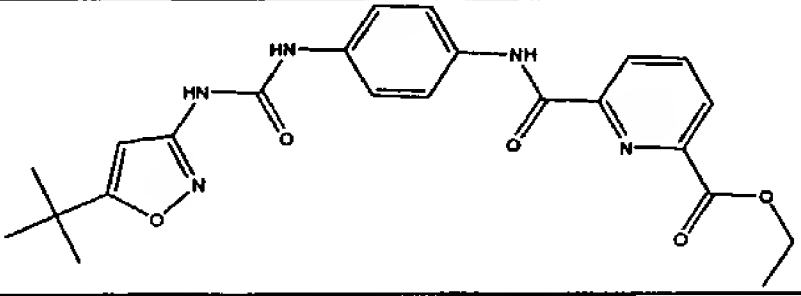
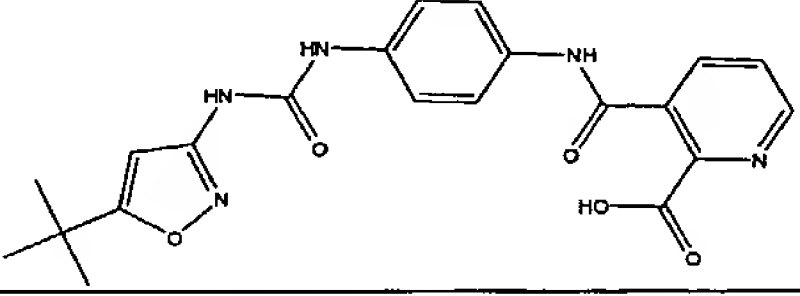
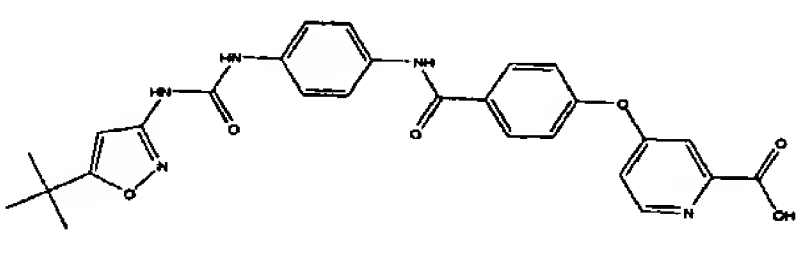
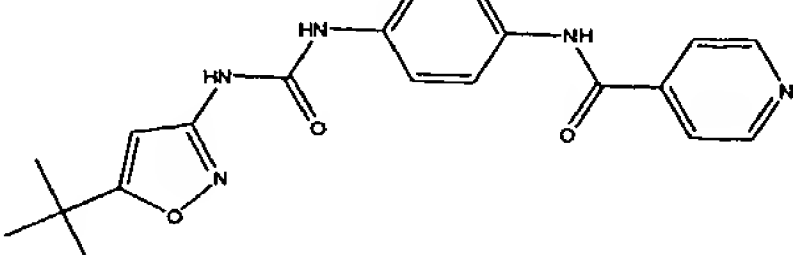
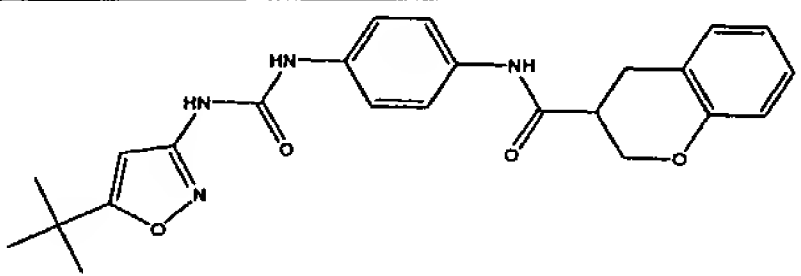
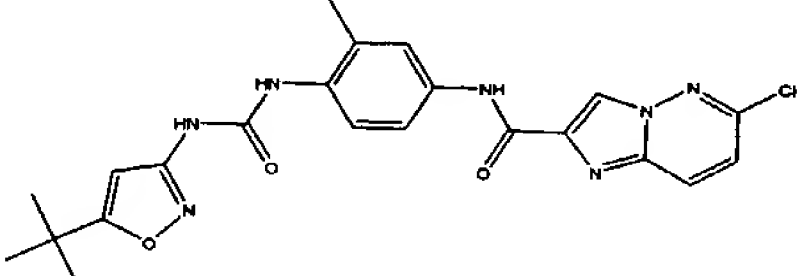
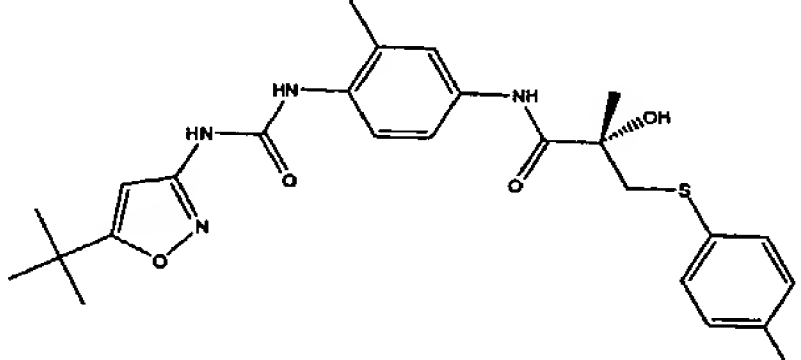
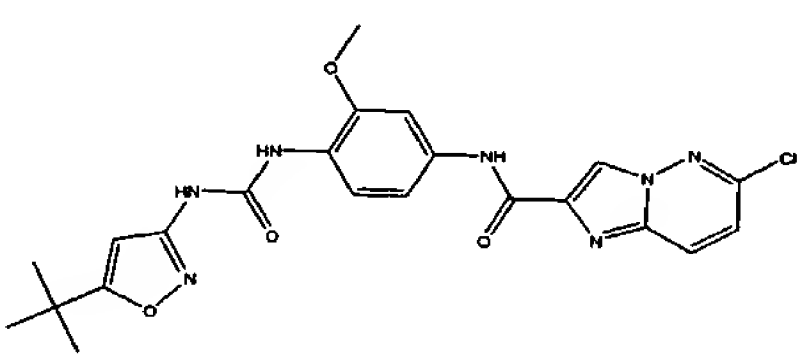
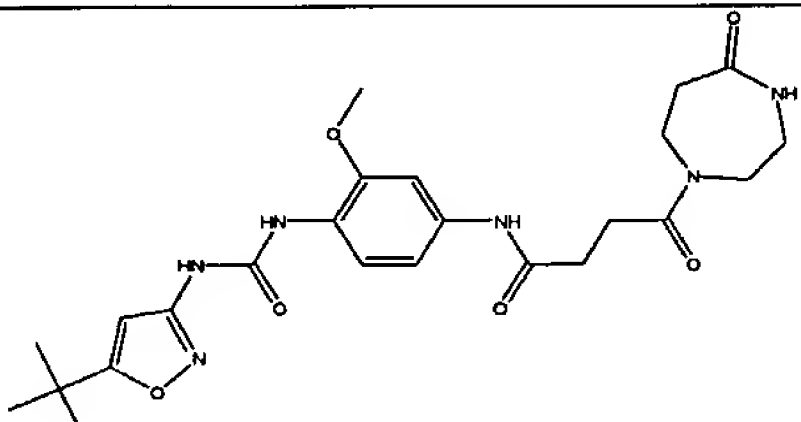
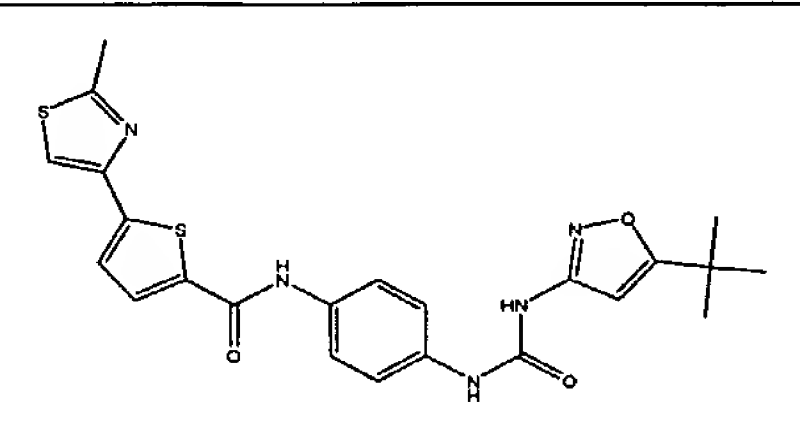
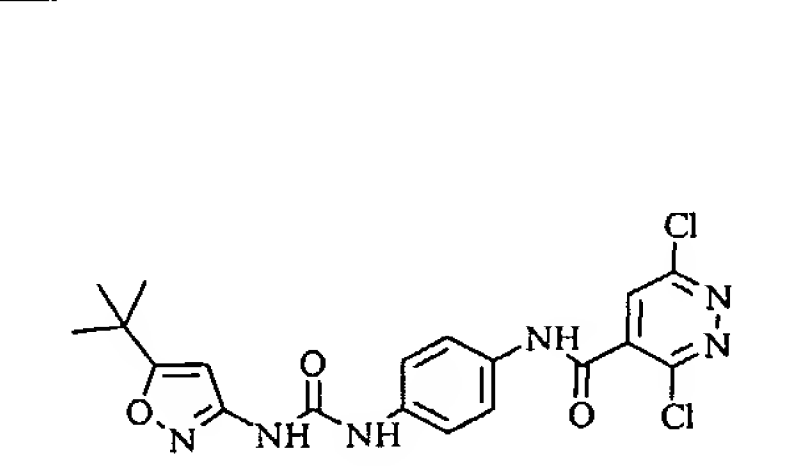
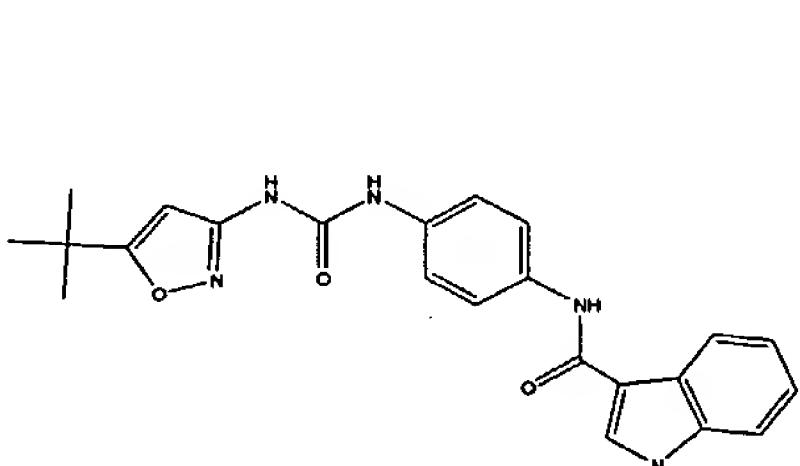
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
N86		N87	
N88		N89	
N90		N91	
N92		N93	
N94		N95	
N96		N97	
N98		N99	
N100		N101	

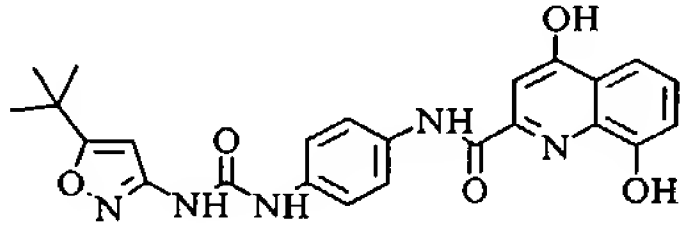
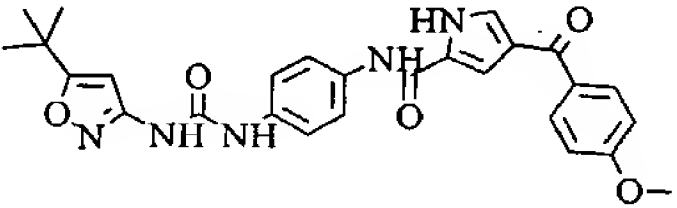
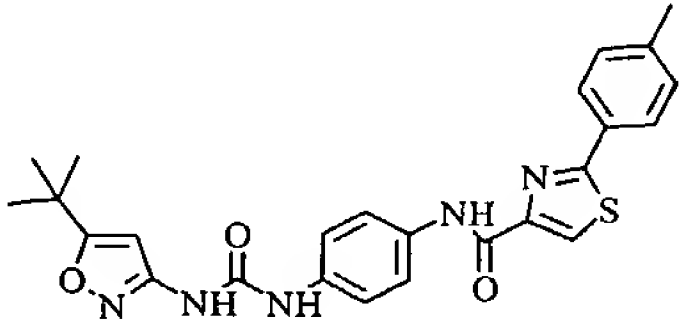
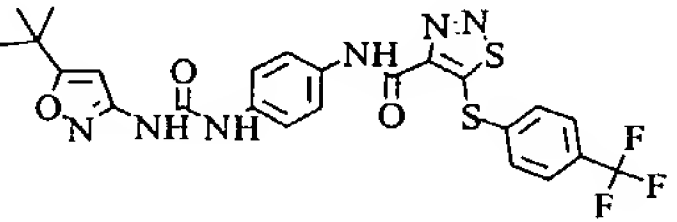
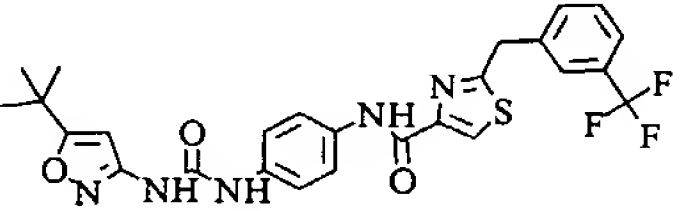
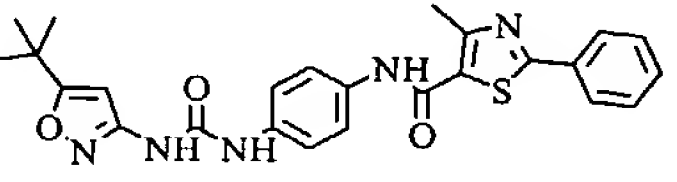
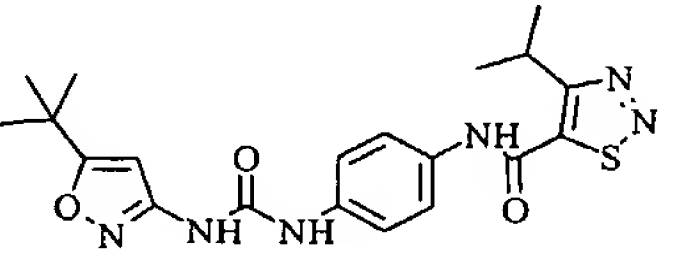
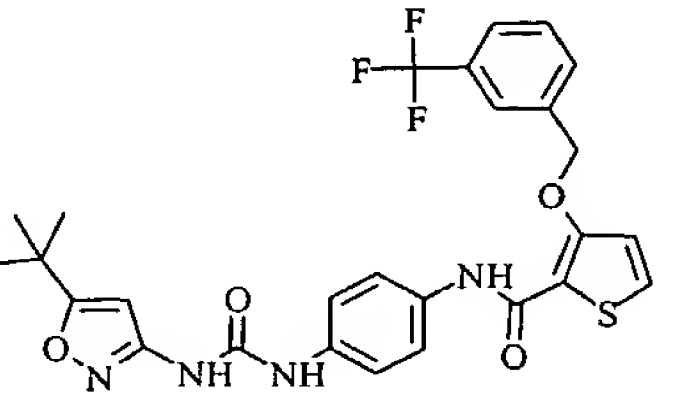
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N106		N107	
N108		N109	
N110		N111	
N112		N113	
N114		N115	

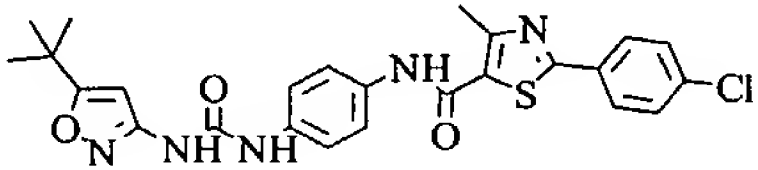
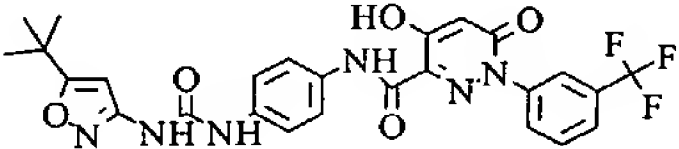
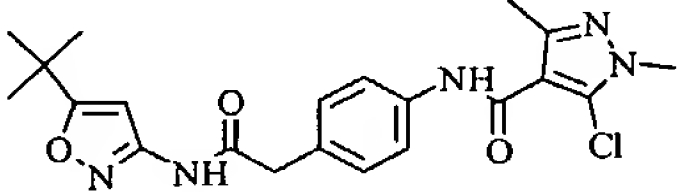
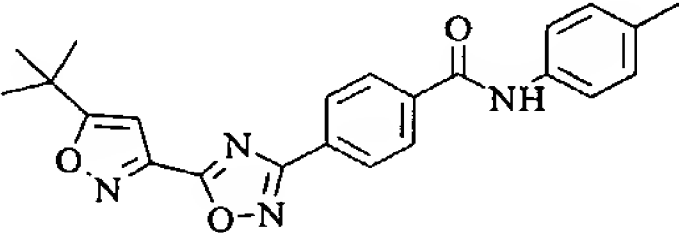
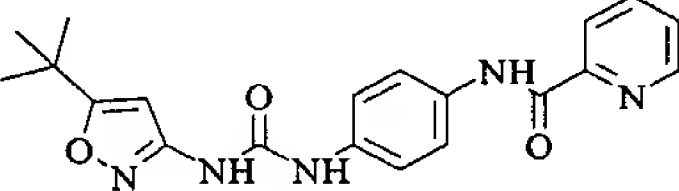
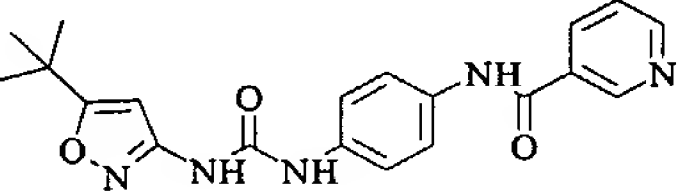
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N118		N119	
N120		N121	
N122		N123	
N124		N125	
N126		N127	

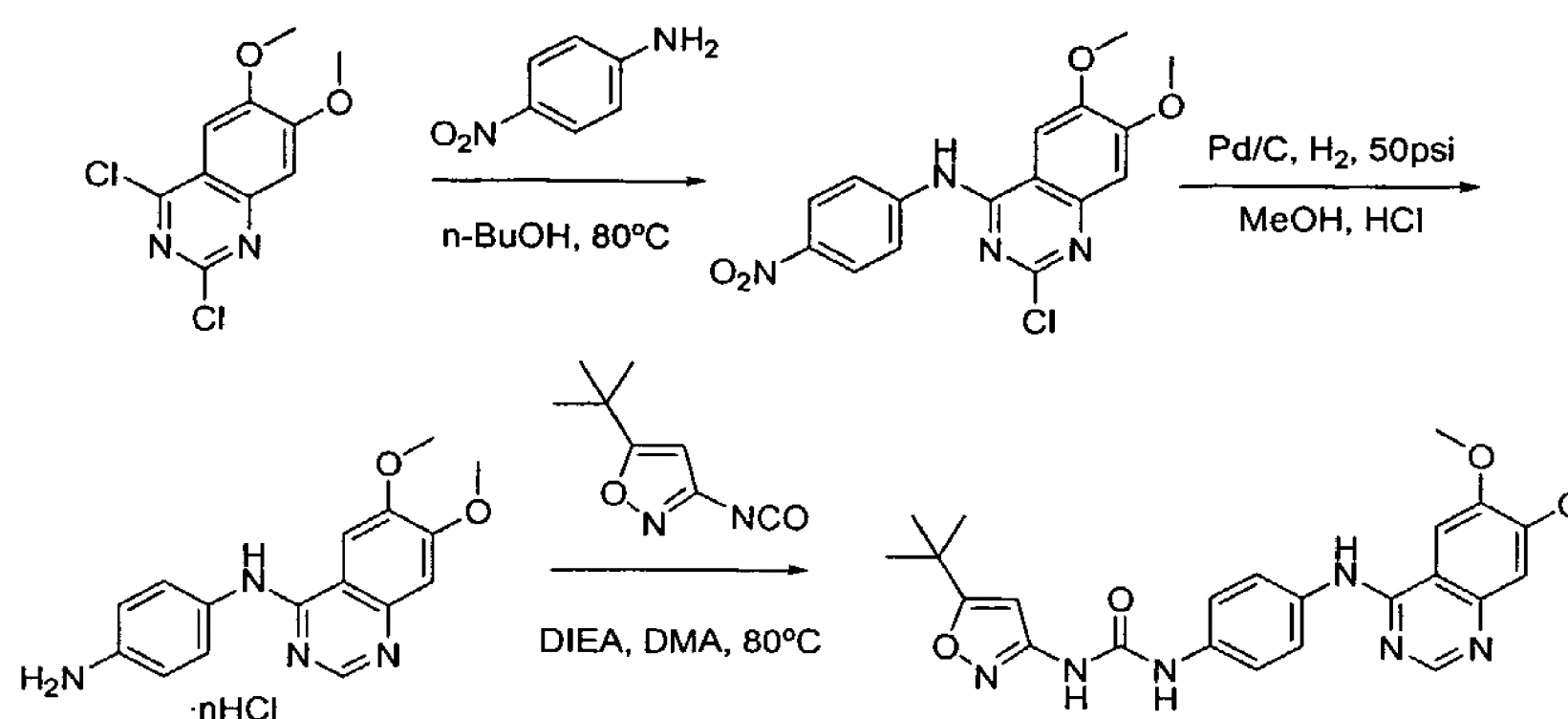
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N130		N131	
N132		N133	
N134		N135	
N136		N137	
N138		N139	
N140		N141	
N142		N143	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
N144		N145	
N146		N147	
N148		N149	
N150		N151	
N152		N153	
N154		N155	
N156		N157	
N158		N159	
N160		N161	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N164		N165	
N166		N167	
N168		N169	
N170		N171	
N172		N173	
N174		N175	

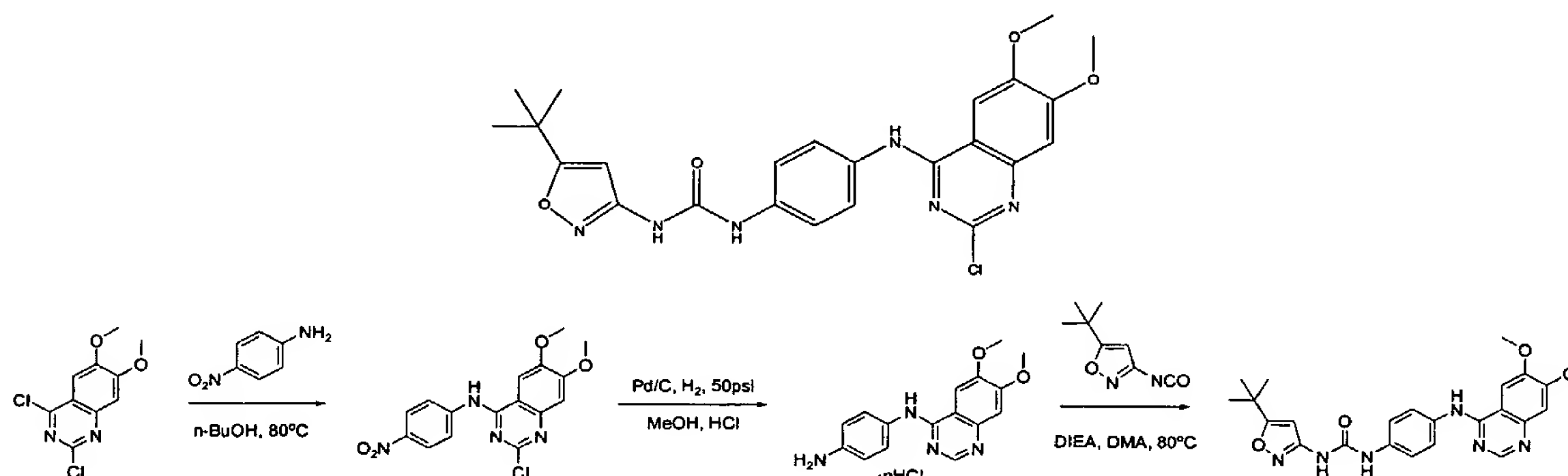
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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N178		N179	
N180		N181	
N182		N183	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
N184		N185	
N186		N187	
N188		N189	

Example O: Synthesis of Compounds with Amine Linkers

Dichloro-dimethoxyquinazoline was heated 3h at 80°C with one equivalent p-nitroaniline in n-butanol. After cooling to room temperature, isopropanol was added and the insoluble product was collected by filtration. Reduction was accomplished using 10%Pd/C in methanol at 50psi in the presence of hydrochloric acid. The resulting aniline was reacted with the oxazole isocyanate in DMA at 80°C in the presence of DIEA. The urea product was purified by HPLC.

Synthesis of Compound O1: 1-(4-(2-chloro-6,7-dimethoxyquinazolin-4-ylamino)phenyl)-3-(5-tert-butylisoxazol-3-yl)urea

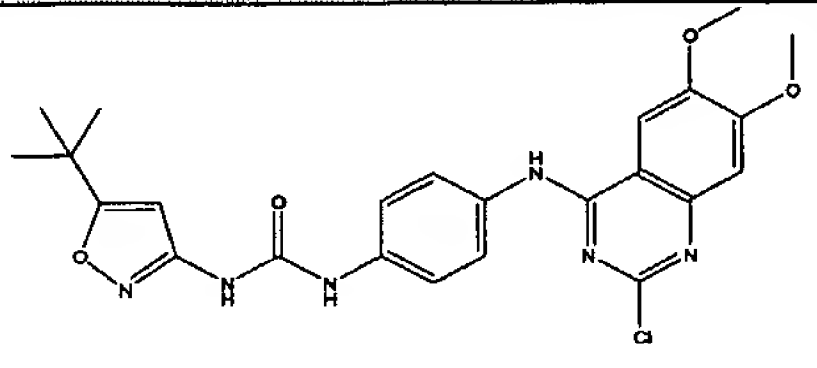
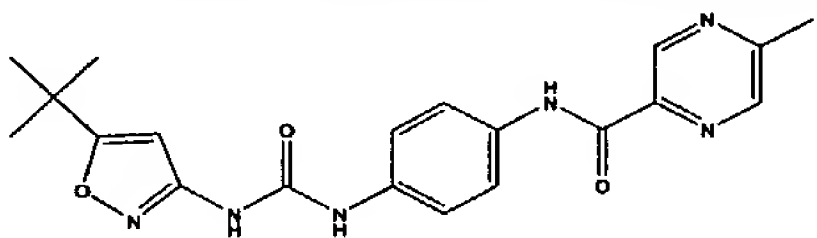
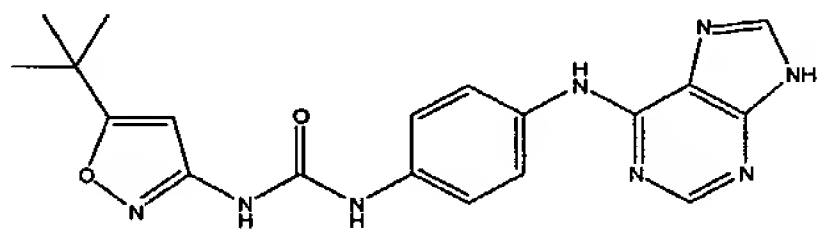
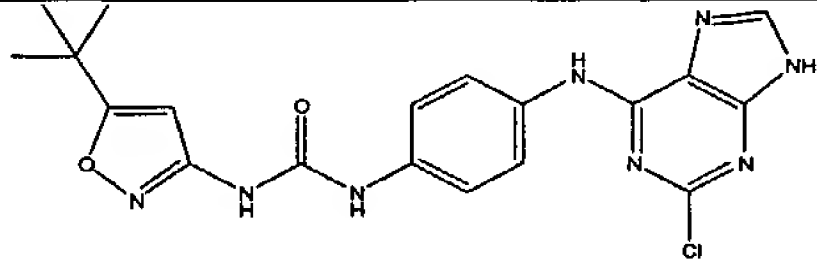
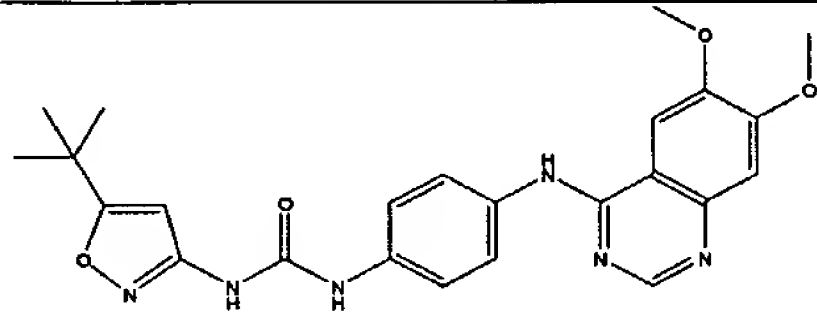
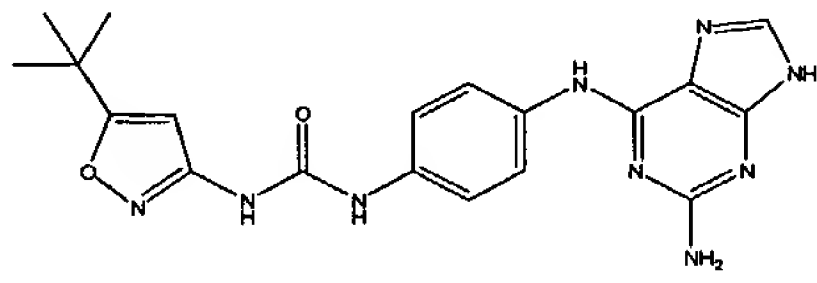
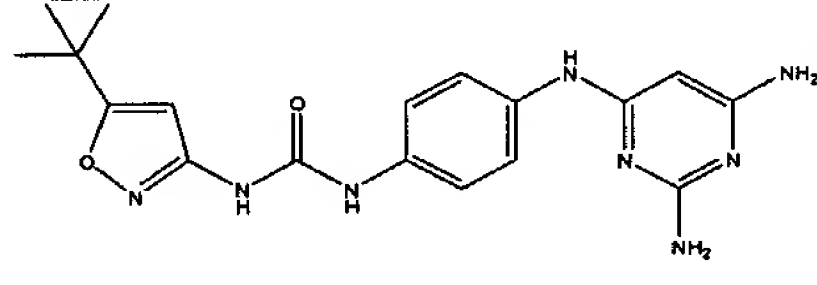
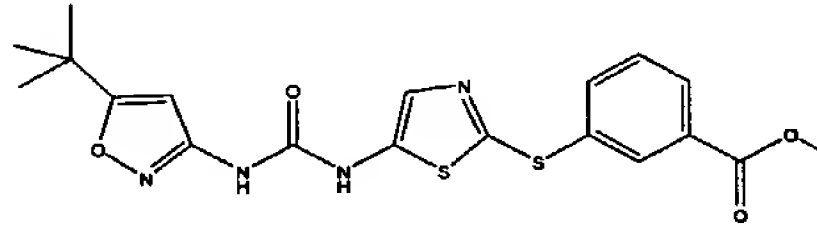
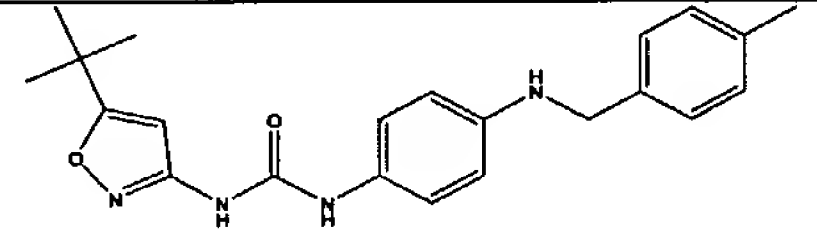
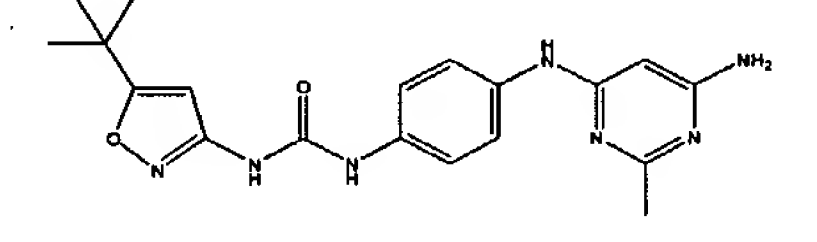


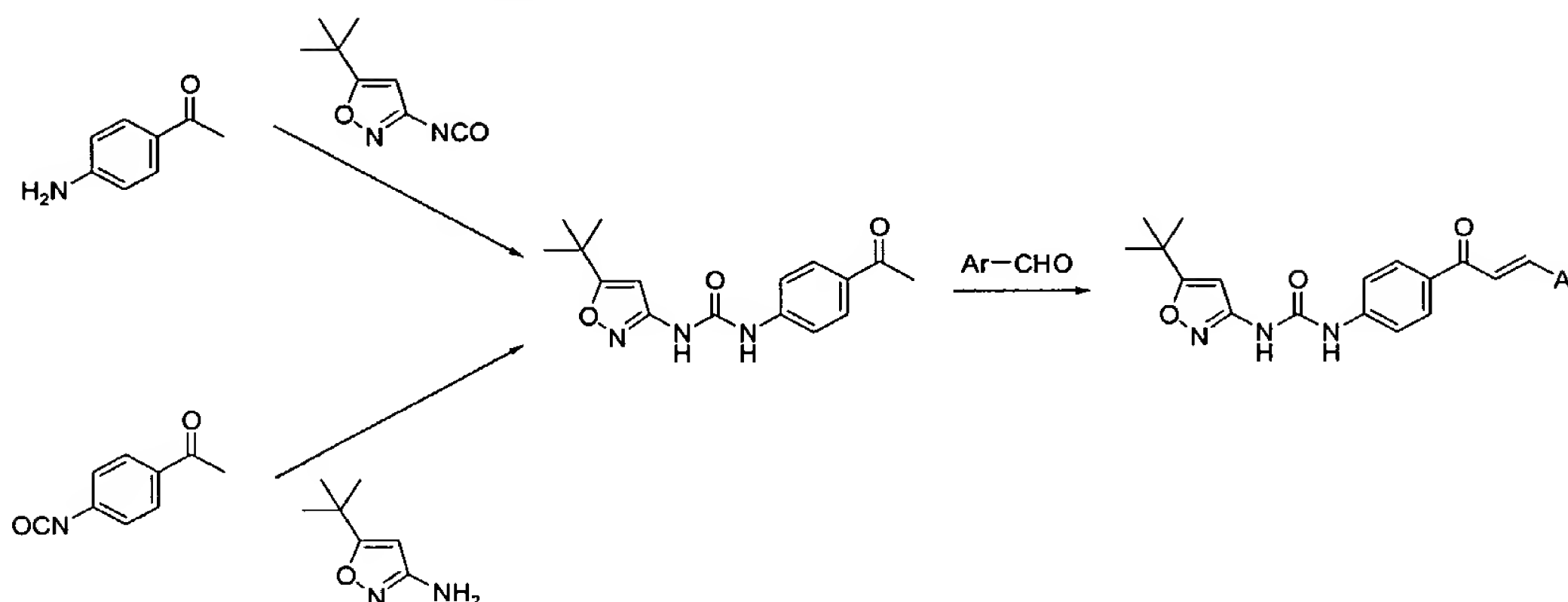
Dichloro-dimethoxyquinazoline was heated 3h at 80°C with one equivalent p-nitroaniline in n-butanol. After cooling to room temperature, isopropanol was added and the insoluble product was collected by filtration. Reduction was accomplished using 10%Pd/C in methanol at 50psi in the presence of hydrochloric acid. The resulting aniline was reacted with the oxazole isocyanate in DMA at 80°C in the presence of DIEA. The urea product was purified by HPLC.

Compounds O2 through O10 were synthesized in a manner analogous to Compound O1

using similar starting materials and reagents. The structures are shown below in Table O:

Table O

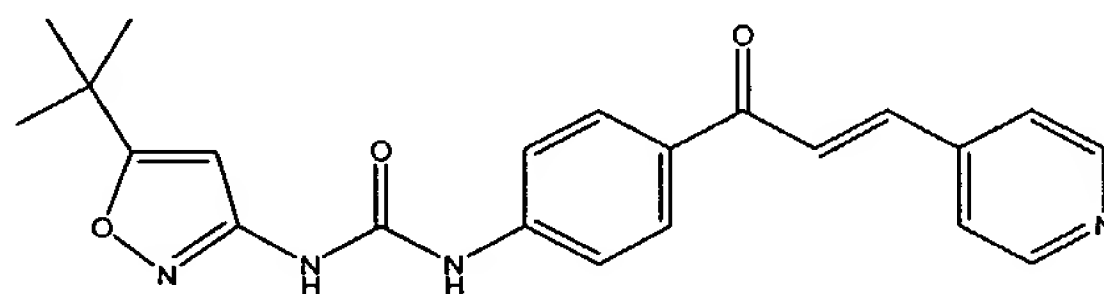
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
O1		O2	
O3		O4	
O5		O6	
O7		O8	
O9		O10	

Example P: Synthesis of Chalcones

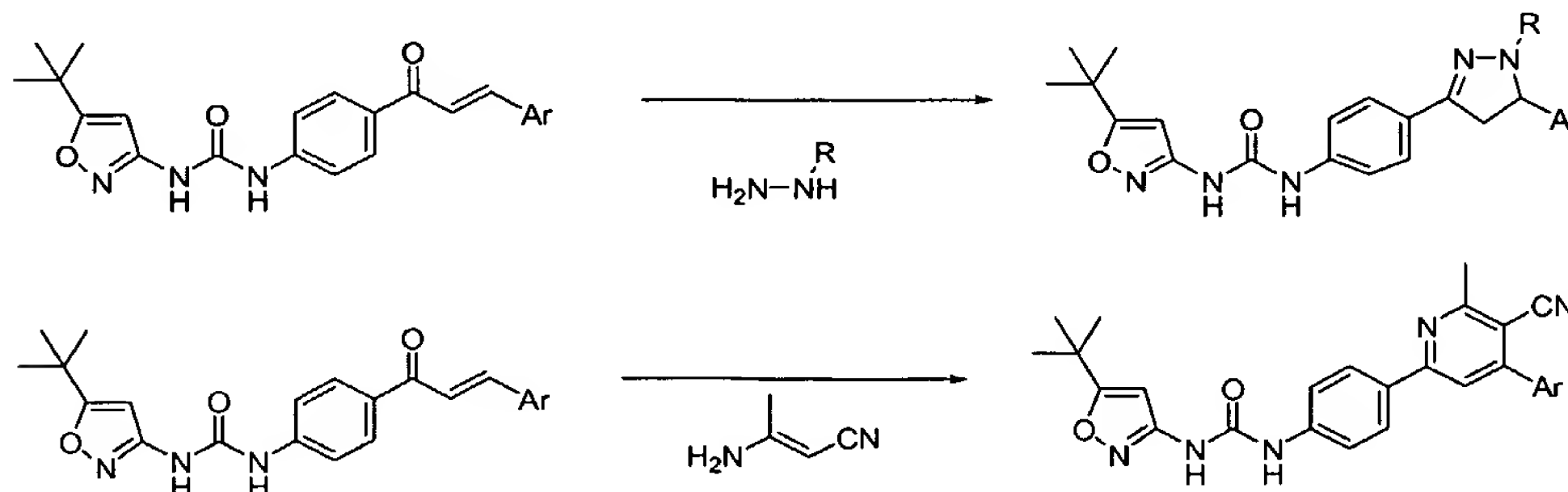
Acetylphenylurea (obtained from either reacting p-aminoacetophenone with oxazole isocyanate in toluene or reacting p-acetylphenyl isocyanate with oxazole amine in toluene) was reacted with e.g. 4-pyridine carboxaldehyde analogous to a literature procedure (Zhang *et al.*, *Chem. Lett.* 2003, 32, 966-967).

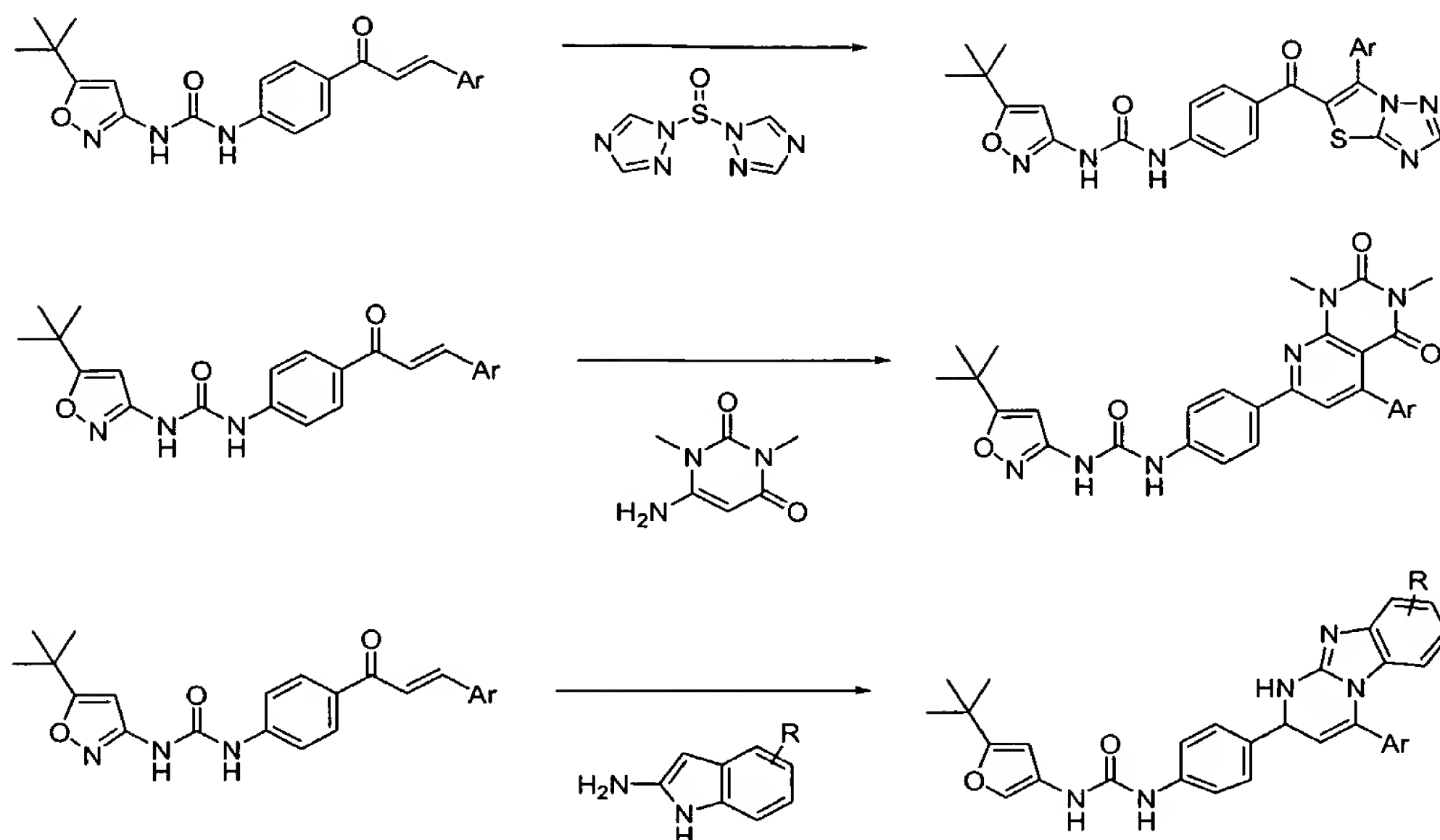
Chalcone intermediates were further modified according to procedures described in the literature. See Powers *et al.*, *Tetrahedron*, 1998, 54, 4085-4096; Katritzky *et al.* *Org. Lett.* 2000, 2, 429-431.

Compound P1: 1-(5-isopropylisoxazol-3-yl)-3-(4-((E)-3-(pyridin-4-yl)acryloyl)phenyl)urea

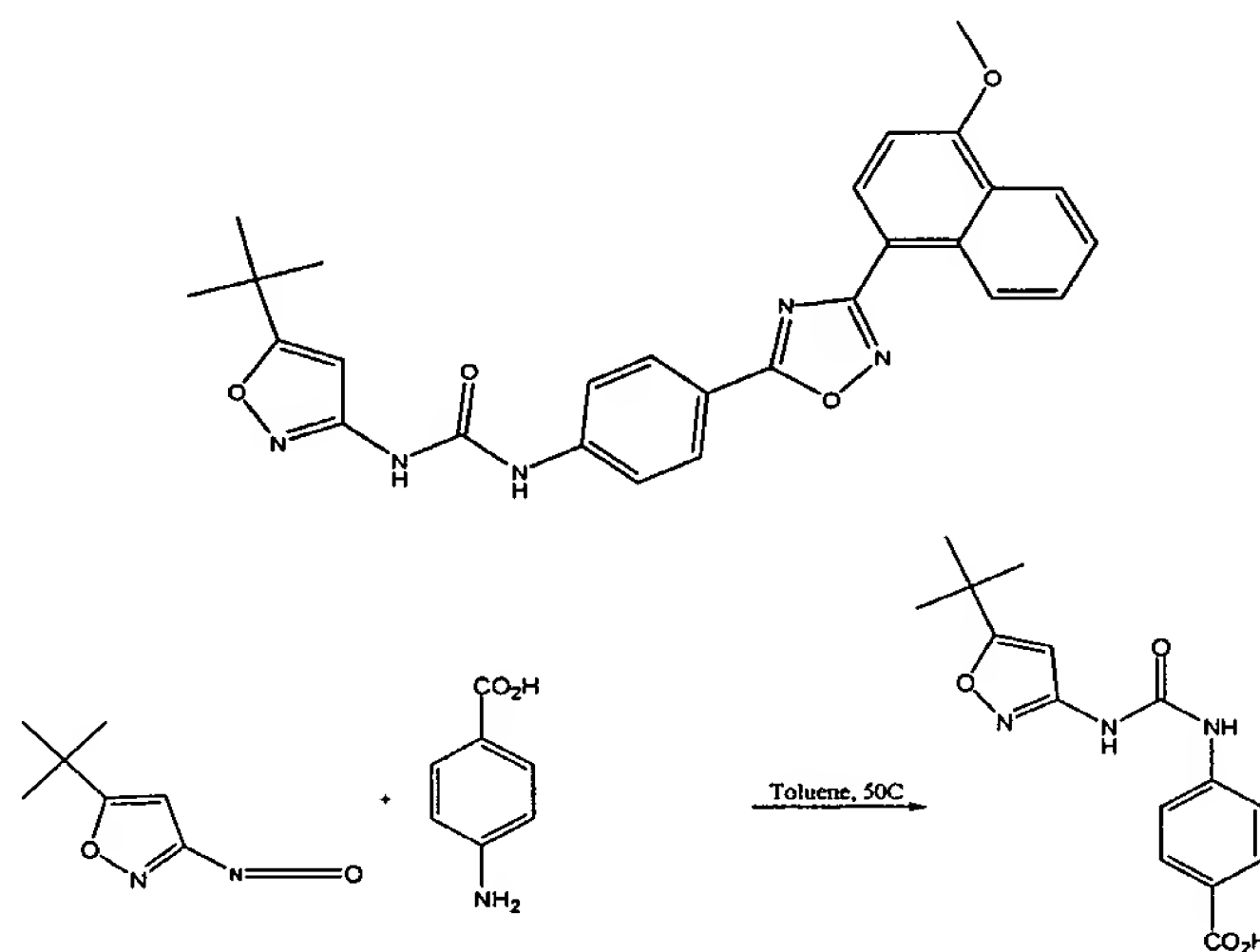


Compound P1 was synthesized in the manner outlined above.

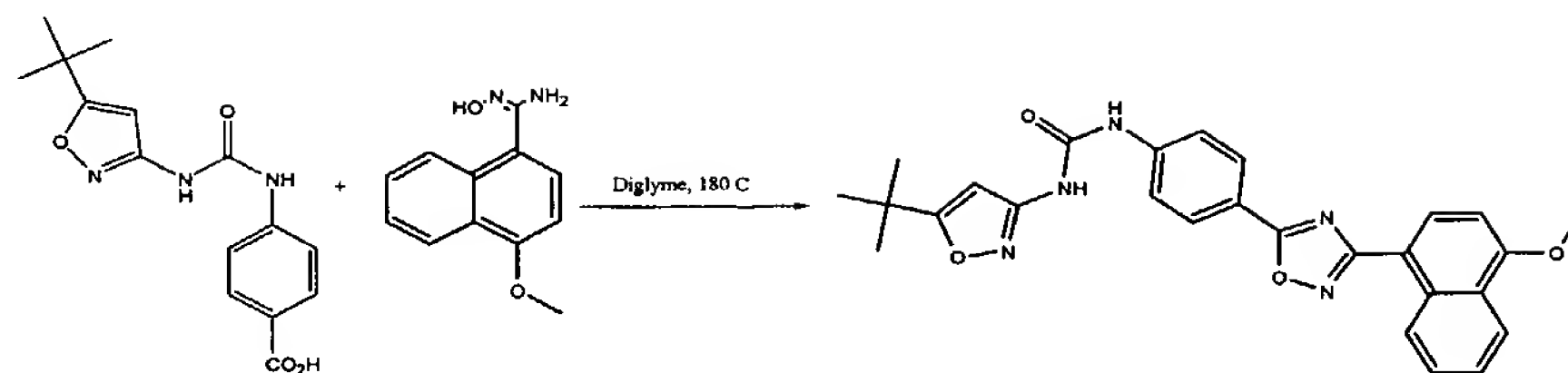
Synthesis of Chalcone Derivatives



Synthesis of Compound P2: 1-(5-tert-butylisoxazol-3-yl)-3-(4-(3-(1-methoxynaphthalen-4-yl)-1,2,4-oxadiazol-5-yl)phenyl)urea



To a flask 5-tert-Butyl-3-isocyanato-isoxazole (242mg, 1eq) 4-aminobenzoic acid (159mg, 1eq) was added and dissolved in toluene. The reaction was allowed to stir at 50°C for three hours. The solvent removed and the mixture was purified by HPLC. Yield: 188mg (47%)

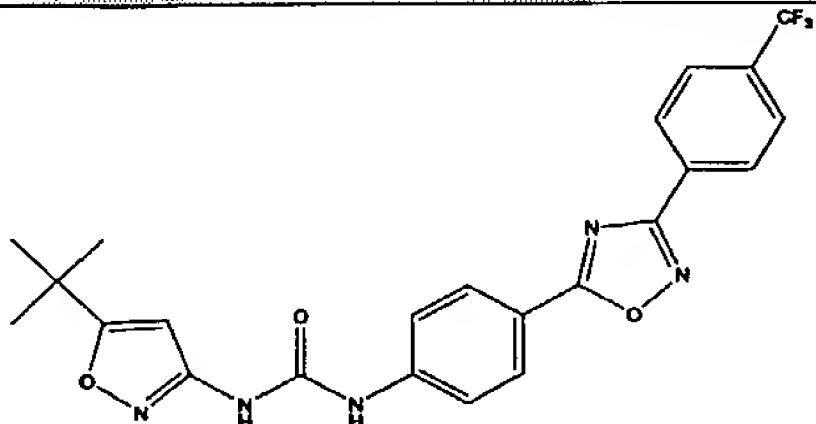
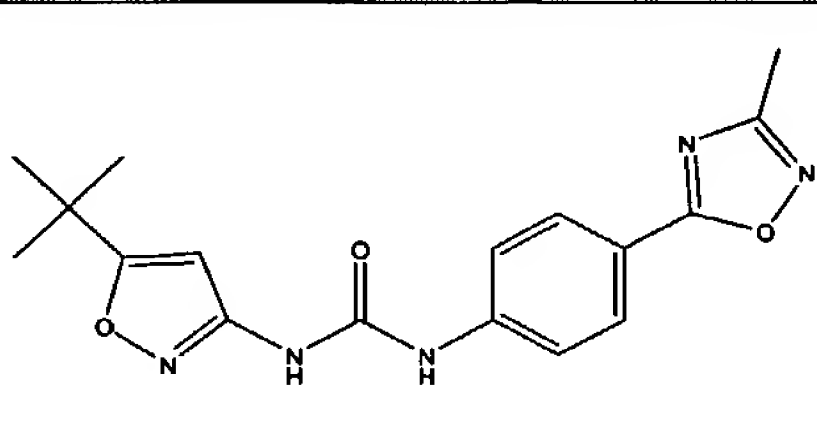


5 N-Hydroxy-4-methoxy-naphthalene-1-carboxamidinium (1g) and 4-[3-(5-tert-Butyl-isoxazol-3-yl)-ureido]-benzoic acid (1 eq) were refluxed in diglyme (5 mL) for 24h and then purified to give 100mg of 1-(5-tert-Butyl-isoxazol-3-yl)-3-{4-[3-(4-methoxy-naphthalen-1-yl)-[1,2,4]oxadiazol-5-yl]-phenyl}-urea.

Compounds P3 through P9 were synthesized in a manner analogous to Compound P2 using similar starting materials and reagents. The structures are shown below in Table P:

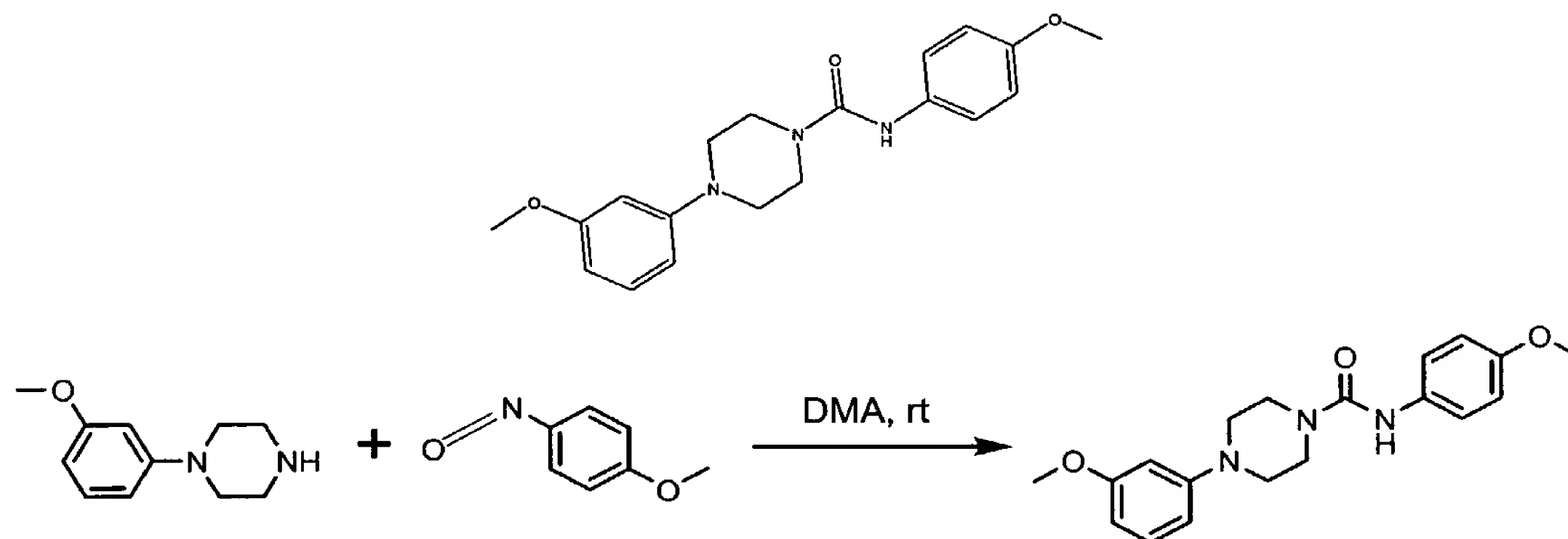
Table P

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
P2		P3	
P4		P5	
P6		P7	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
P8		P9	

Example Q: Synthesis of Compounds Containing Heterocycloalkyl Groups

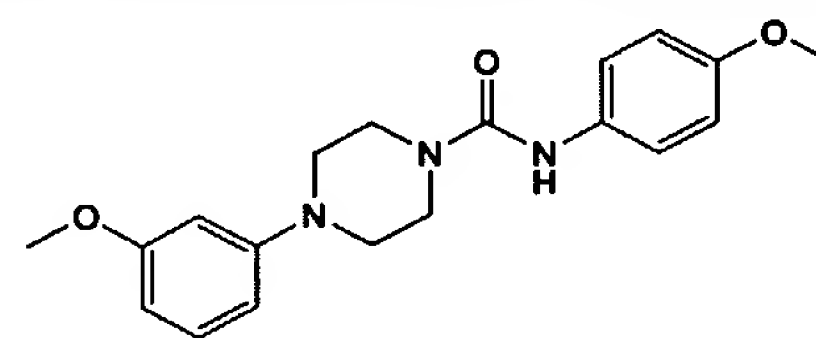
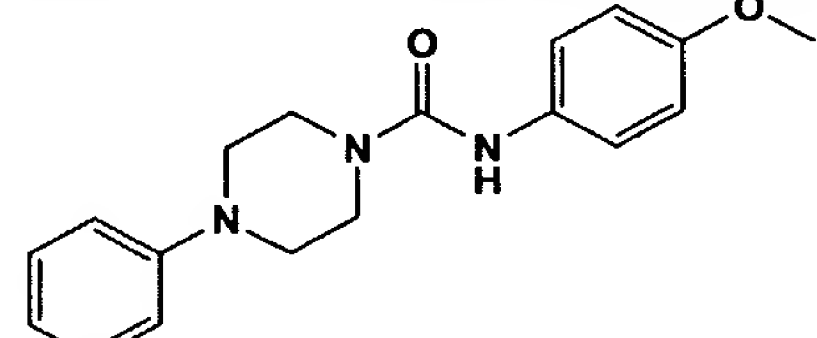
Synthesis of Compound Q1: 4-(3-methoxyphenyl)-N-(4-methoxyphenyl)piperazine-1-carboxamide

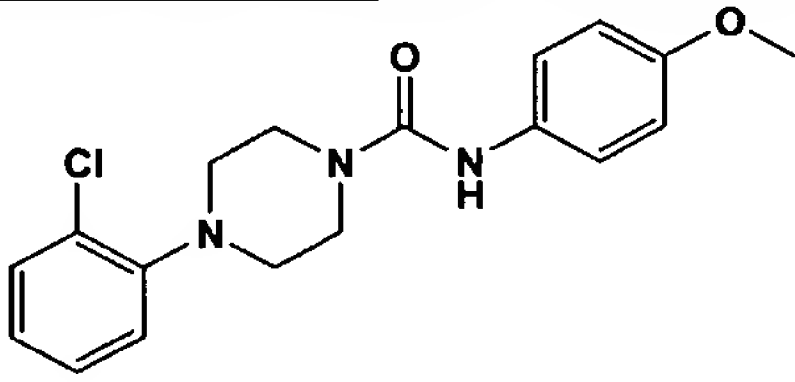
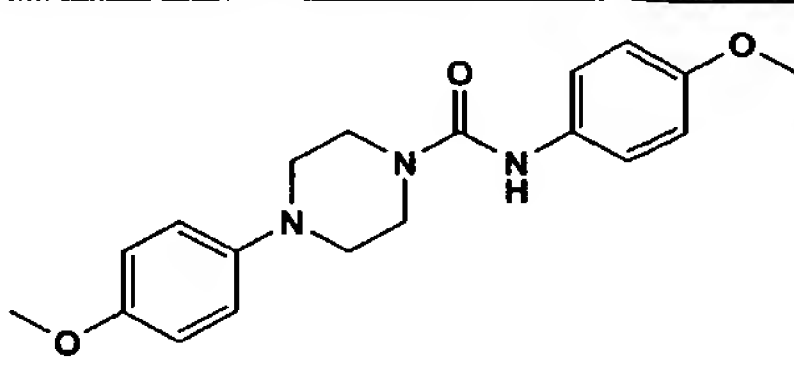
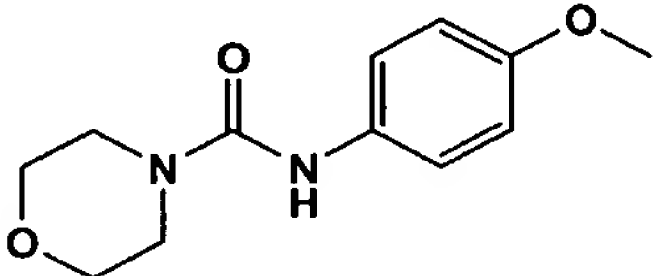
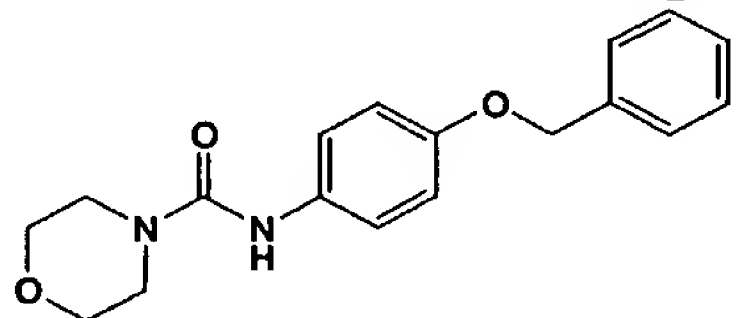
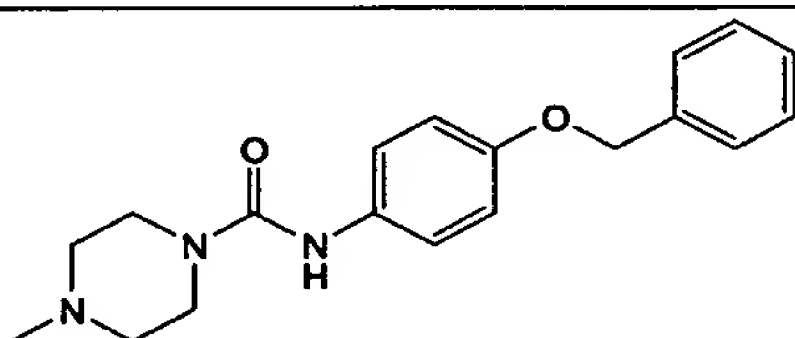
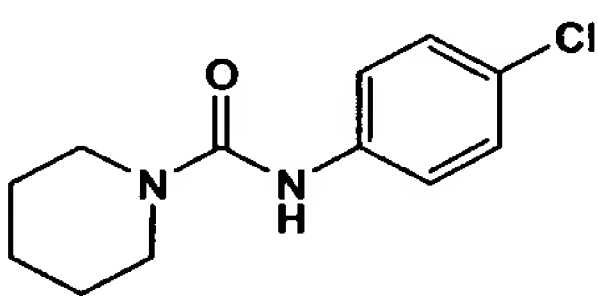
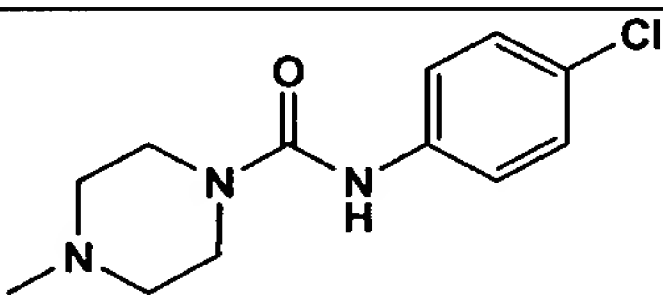
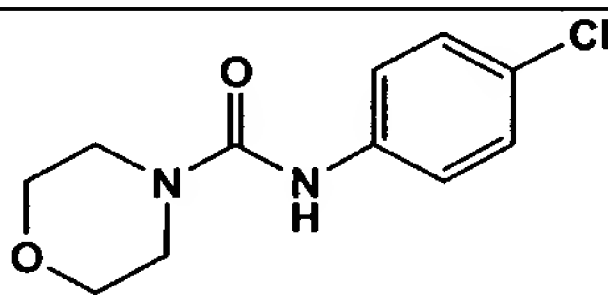
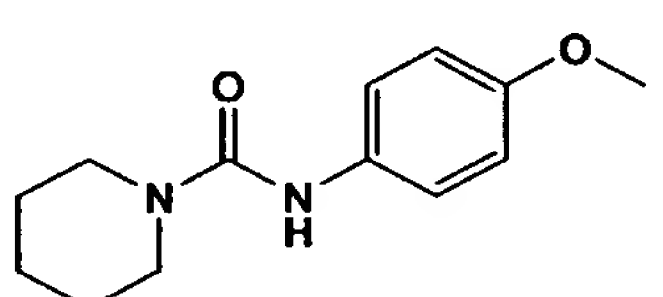
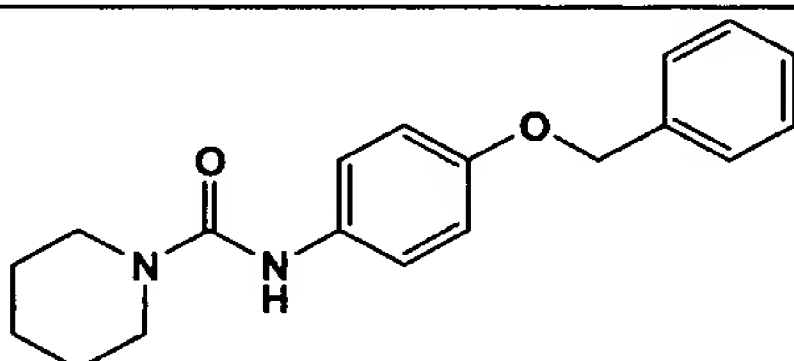
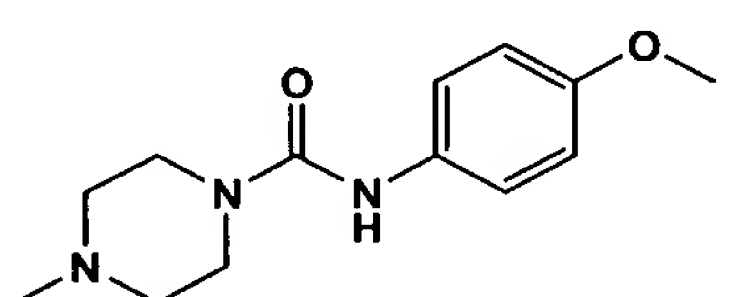
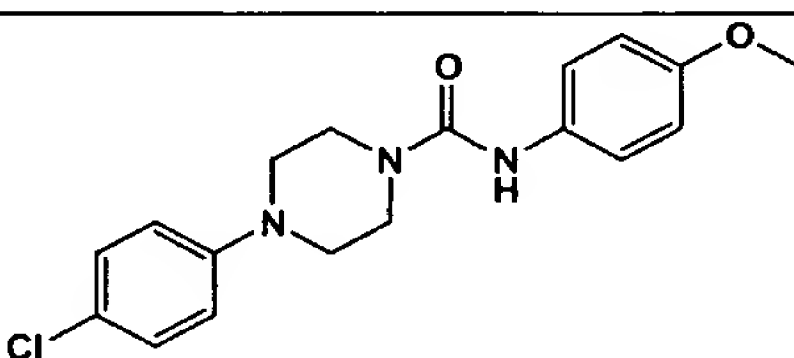
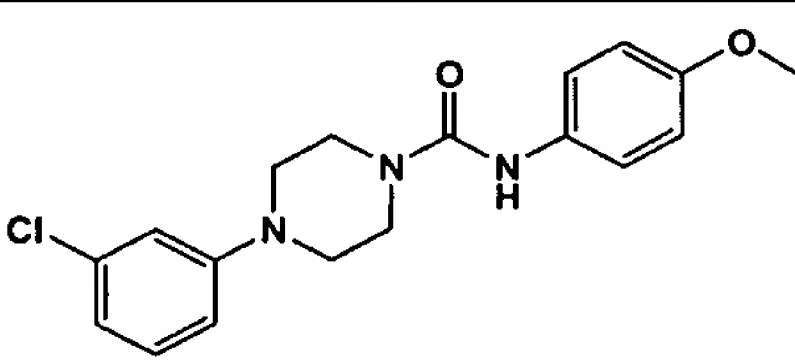
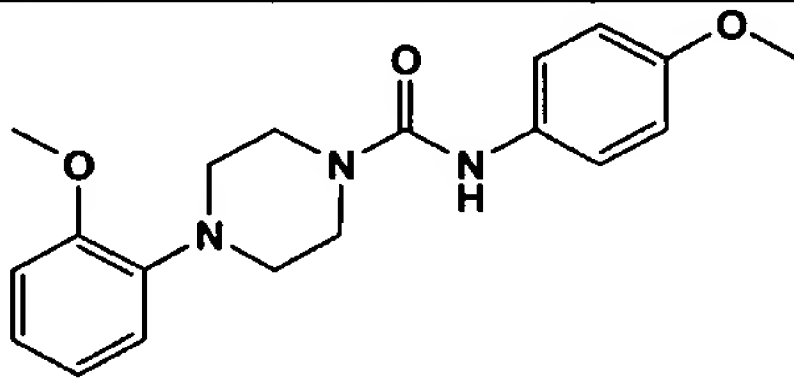


Commercially available isocyanides were reacted with a secondary amine in toluene or DMA (1ml) with triethyl amine (0.2 mL) at room temperature or 50 C overnight. The solvent was removed and the compound purified by HPLC.

10 Compounds Q2 through Q27 were synthesized in a manner analogous to Compound Q1 using similar starting materials and reagents. The structures are shown below in Table Q:

Table Q

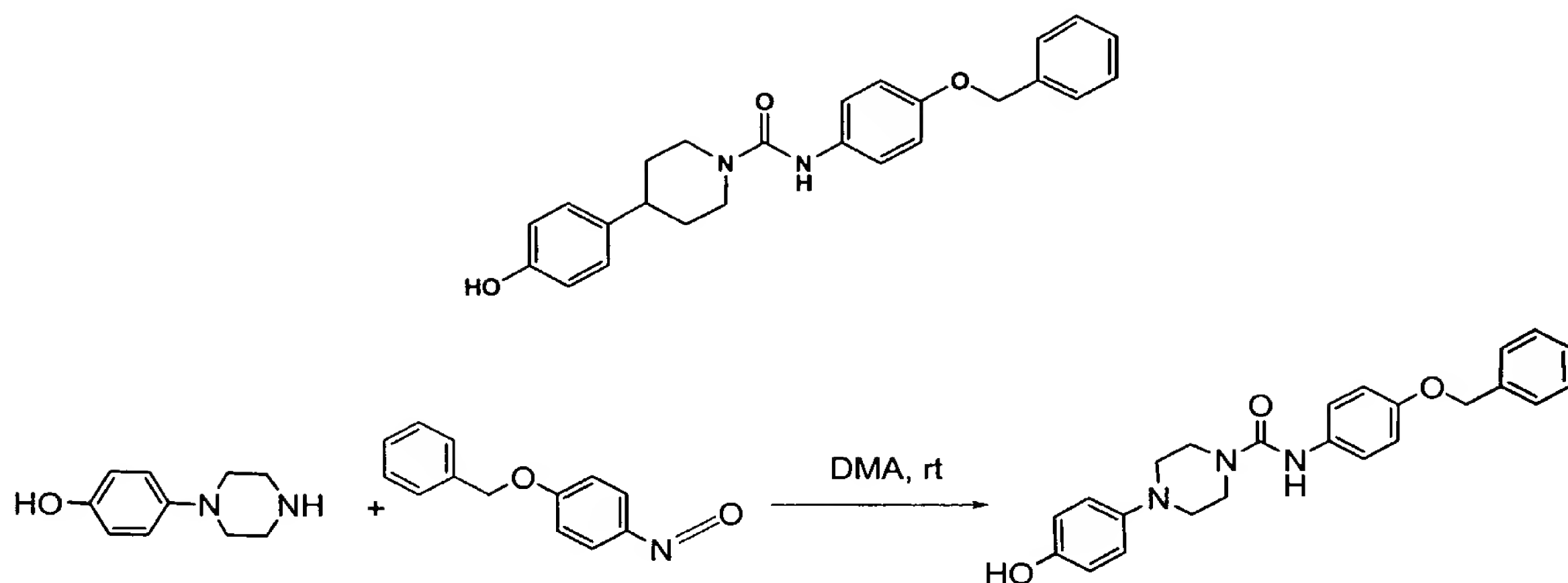
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
Q1		Q2	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
Q3		Q4	
Q5		Q6	
Q7		Q8	
Q9		Q10	
Q11		Q12	
Q13		Q30	
Q31		Q32	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
Q17		Q18	
Q19		Q20	
Q21		Q22	
Q23		Q24	
Q25		Q26	
Q27			

Example R: Synthesis of Compounds Containing Heterocycloalkyl Groups with Ether Linkers

Synthesis of Compound S1: N-(4-(benzyloxy)phenyl)-4-(4-hydroxyphenyl)piperidine-1-carboxamide

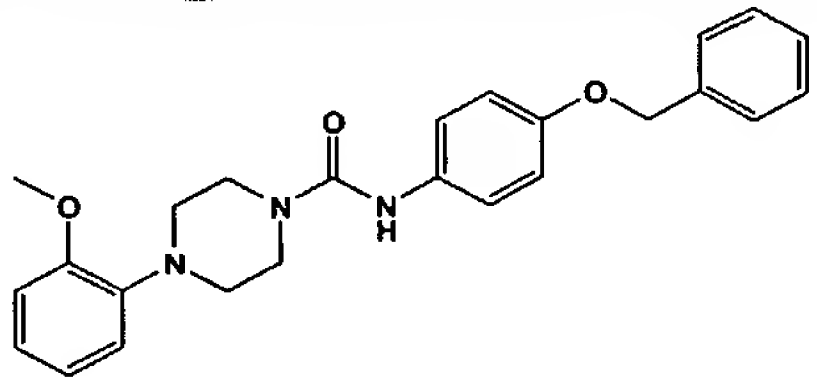
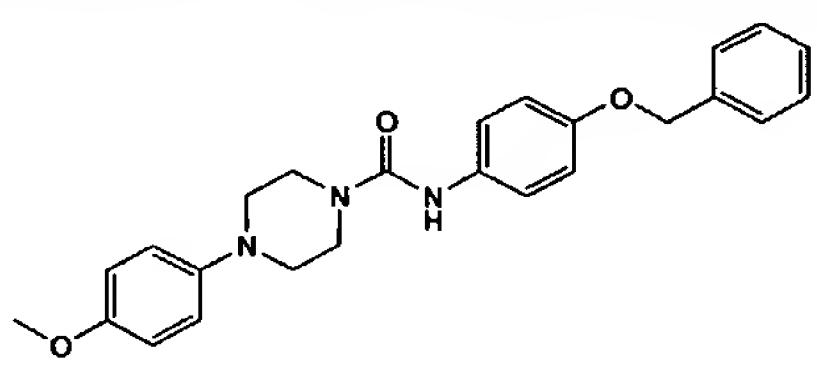
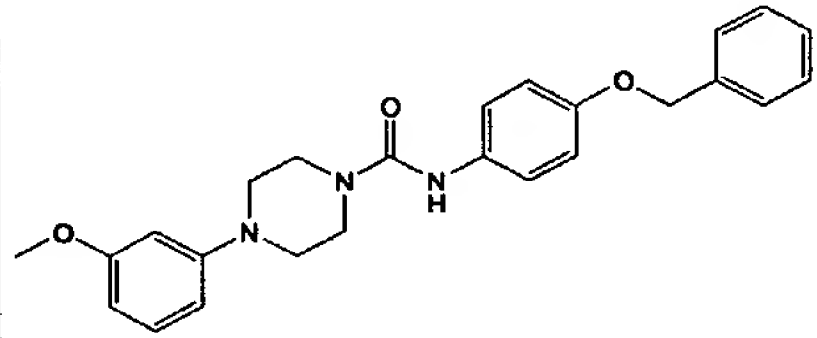


Commercially available isocyanides were reacted with a secondary amine in toluene or DMA (1ml) with triethyl amine (0.2 mL) at room temperature or 50 C overnight. The solvent was removed and the compound purified by HPLC.

Compounds R2 through R9 were synthesized in a manner analogous to Compound R1 using similar starting materials and reagents. The structures are shown below in Table R:

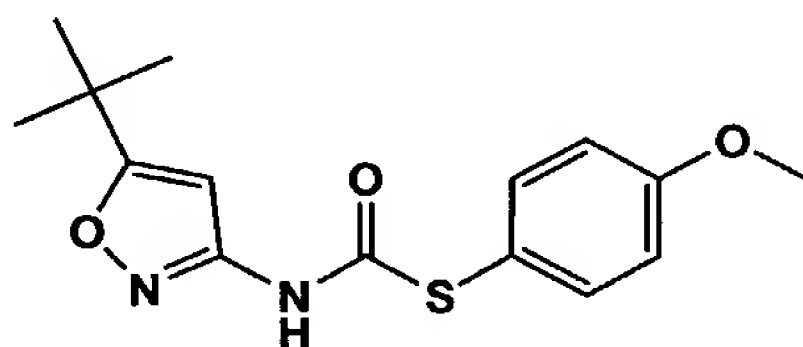
Table R

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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R3		R4	
R5		R6	

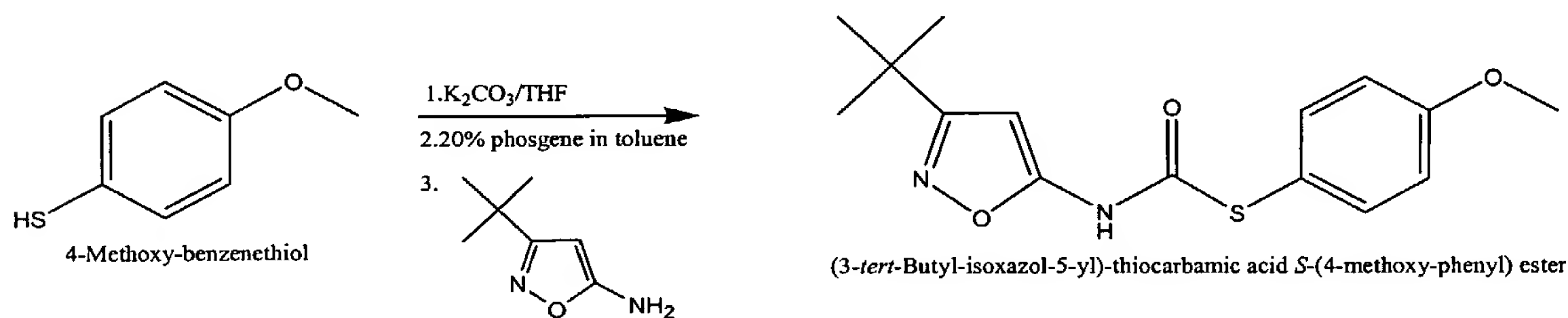
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
R7		R8	
R9			

Example S: Synthesis of Carbamothioates

Synthesis of Compound S1: *S*-4-methoxyphenyl *N*-5-*tert*-butylisoxazol-3-ylcarbamothioate



5 Synthesis of (3-*tert*-Butyl-isoxazol-5-yl)-thiocarbamic acid *S*-(4-methoxy-phenyl) ester:



A mixture of 4-Methoxy-benzenethiol (0.20g, 1eq) and potassium carbonate (0.47g, 2.5eq) in dry THF was allowed to stir at room temperature under argon for an hour. Then the stirred suspension was cooled to 0°C and to it was added drop wise a solution of phosgene (0.17g 1.2eq). The reaction stirred at 0°C for half an hour. Then 3-*tert*-Butyl-isoxazol-5-ylamine (0.20g, 1eq) in THF was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed and extracted with ethyl acetate and water. The organic layer was dried over magnesium sulfate and solvent removed.

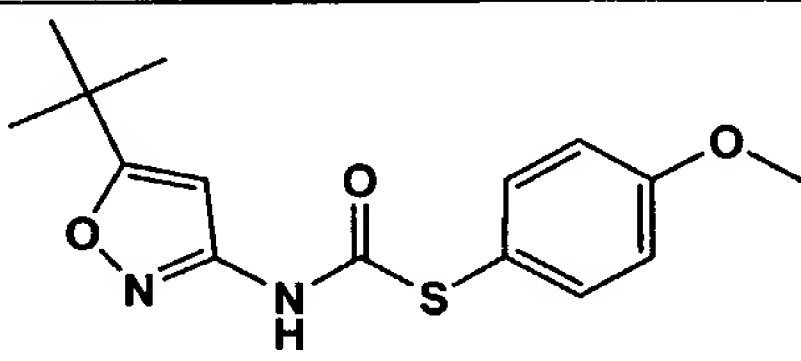
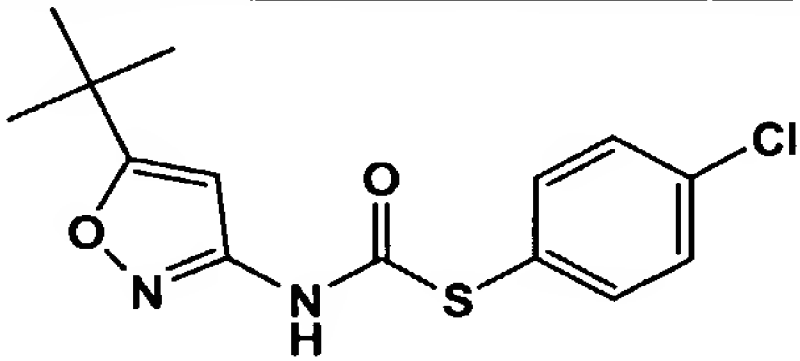
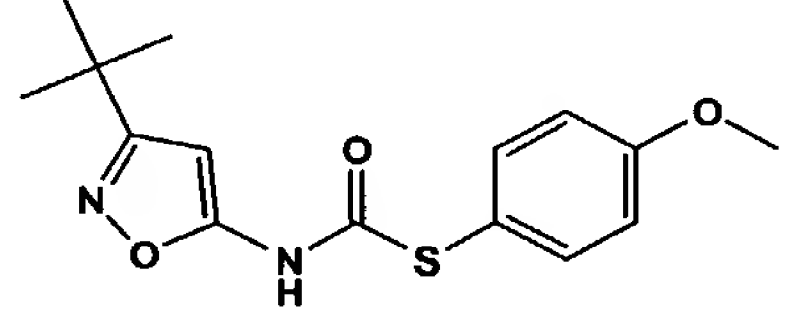
10 It was purified by HPLC. Yield: 157mg (36%), LC/MS [MH⁺] 307.

15

Compounds S2 through S3 were synthesized in a manner analogous to Compound S1

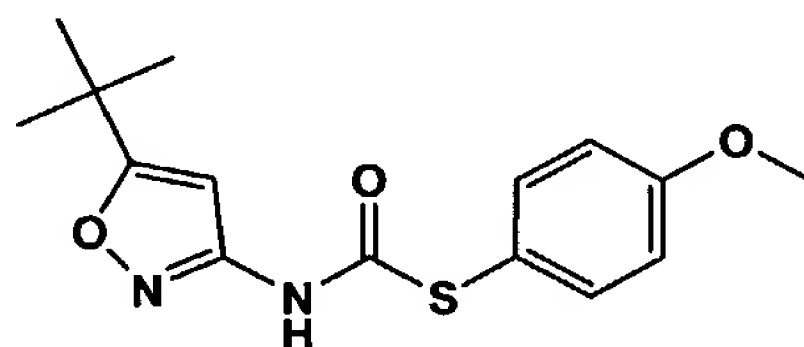
using similar starting materials and reagents. The structures are shown below in Table S:

Table S

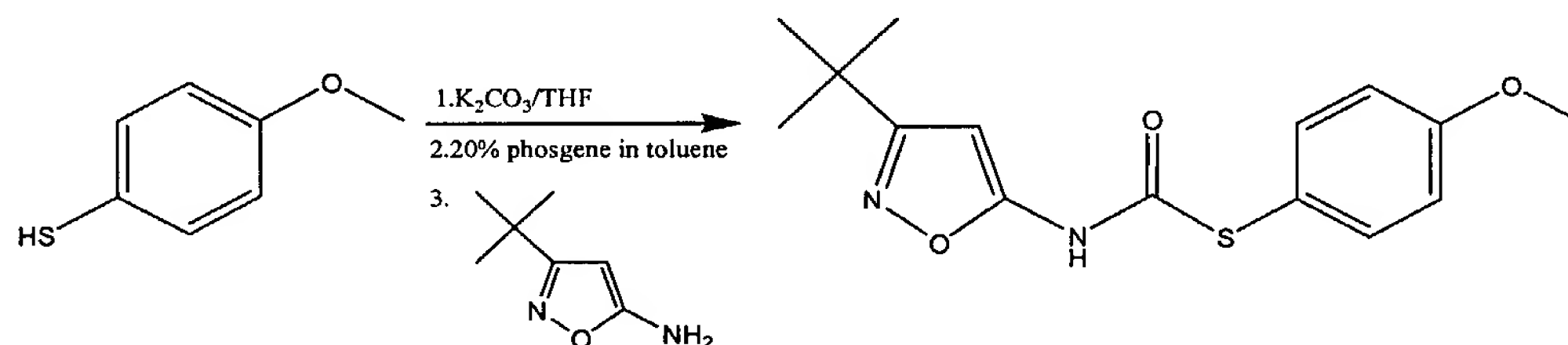
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
S1		S2	
S3			

Example T: Synthesis of Carbamothioates

5 Synthesis of Compound T1: S-4-methoxyphenyl N-5-tert-butylisoxazol-3-ylcarbamothioate



Synthesis of (3-tert-Butyl-isoxazol-5-yl)-thiocarbamic acid S-(4-methoxy-phenyl) ester



10

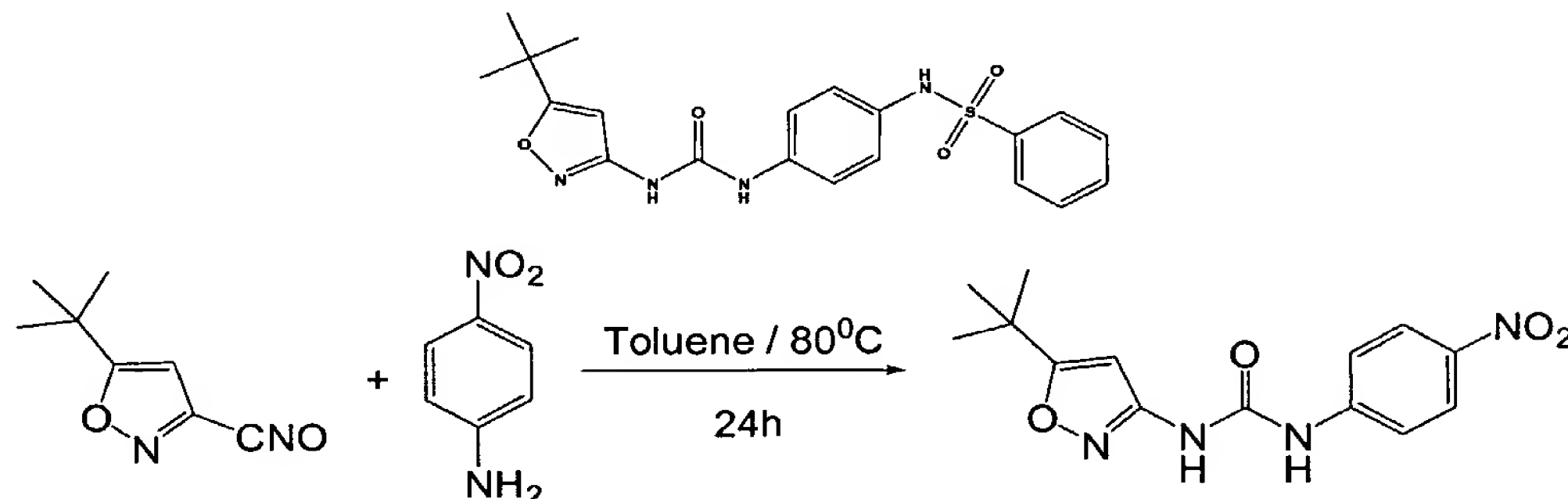
15

A mixture of 4-Methoxy-benzenethiol (0.20g, 1eq) and potassium carbonate (0.47g, 2.5eq) in dry THF was allowed to stir at room temperature under argon for an hour. Then the stirred suspension was cooled to 0°C and to it was added drop wise a solution of phosgene (0.17g 1.2eq). The reaction stirred at 0°C for half an hour. Then 3-tert-Butyl-isoxazol-5-ylamine (0.20g, 1eq) in THF was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed and extracted with ethyl acetate and water. The organic layer was dried over magnesium sulfate and solvent removed.

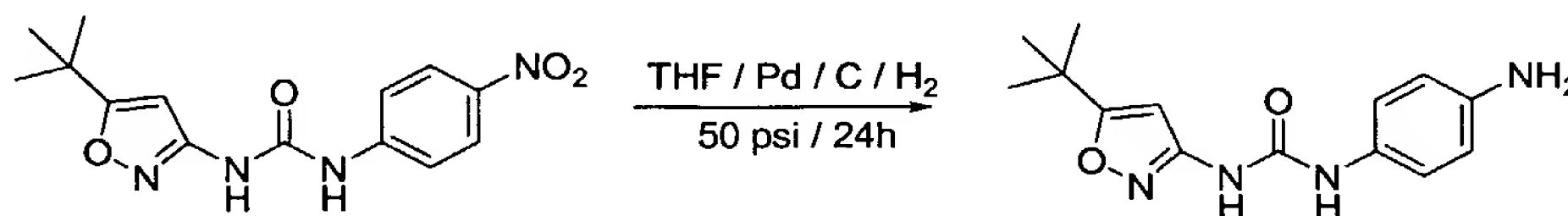
It was purified by HPLC. Yield: 157mg (36%), LC/MS [MH⁺] 307.

Example V: Synthesis of Ureas

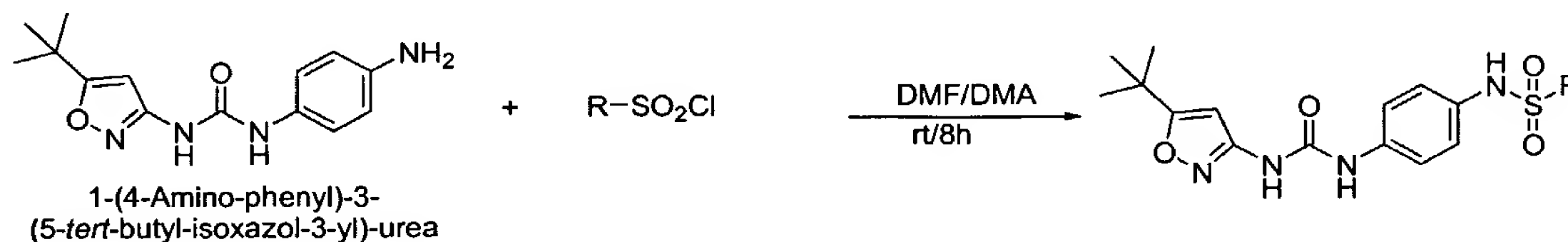
Synthesis of Compound V1:



10 1 gm. (6 mmol) of 5-tert-butyl-isoxazole-3-isocyanate and 0.83gm (6 mmol) 4-nitro-phenylamine were dissolved in 20ml dry toluene and stirred at 80°C for 24h. The resulting suspension was cooled to room temperature and filtered off to give the title compound as a yellow solid. The product was used in the next step without further purification. Yield: 1.7 g (92%), LC/MS [MH⁺] 305.



15 1.5 gm of 1-(5-tert-butyl-isoxazol-3-yl)-3-(4-nitro-phenyl)-urea was dissolved in 50ml THF and 0.1 g of 10% Pd/C was added. The solution was stirred under hydrogen at 50 psi. for 24h than filtered trough Celite pad. The organic solvent was evaporated under vacuum and the resulting residue was triturated with ethyl acetate. Yield: 1.3g (96%), LC/MS [MH⁺] 275.

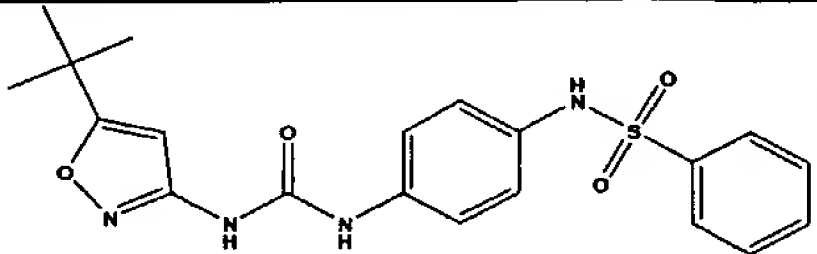
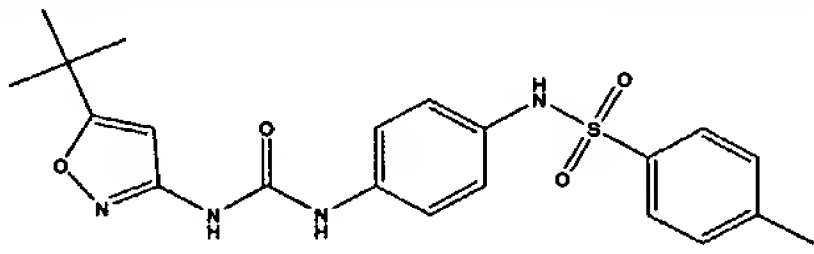
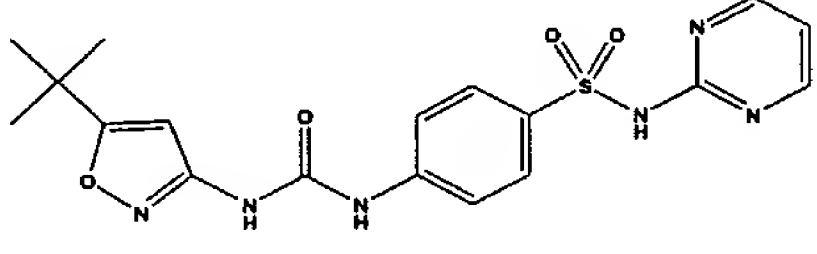
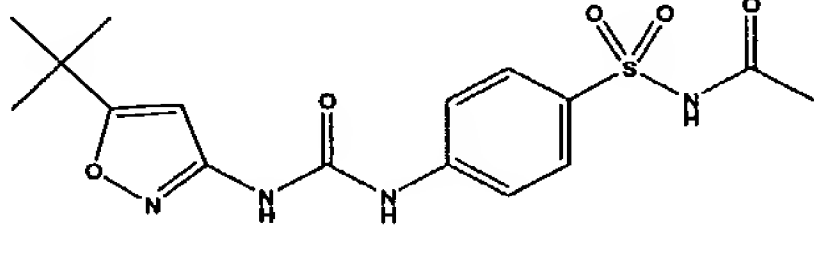


1 equivalent of the substituted sulfonyl chloride and 1 equivalent of the substituted aniline in DMF were added, and the solution stirred at room temperature for 8h. The final product was purified by preparative HPLC.

Compounds V2 through V4 were synthesized in a manner analogous to Compound V1

using similar starting materials and reagents. The structures are shown below in Table V:

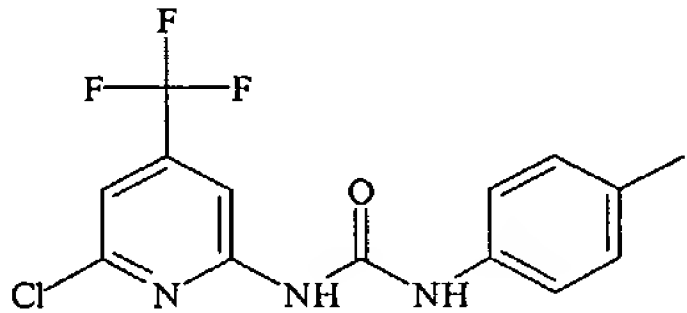
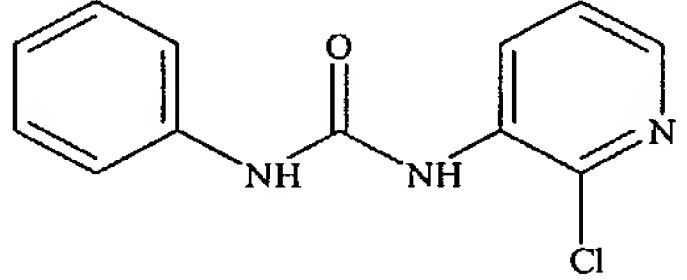
Table V

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
V1		V2	
V3		V4	

Example W:

5 Compounds W1 and W2 were made by procedures know in the art or described herein.

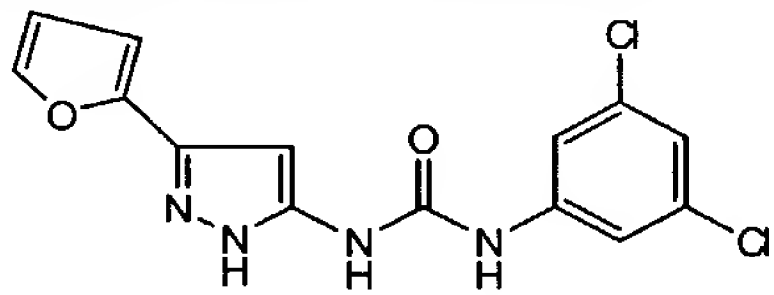
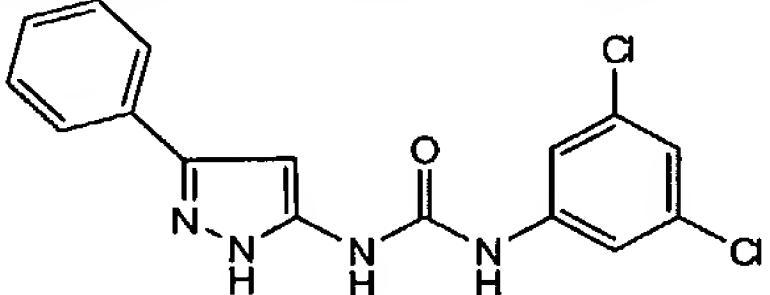
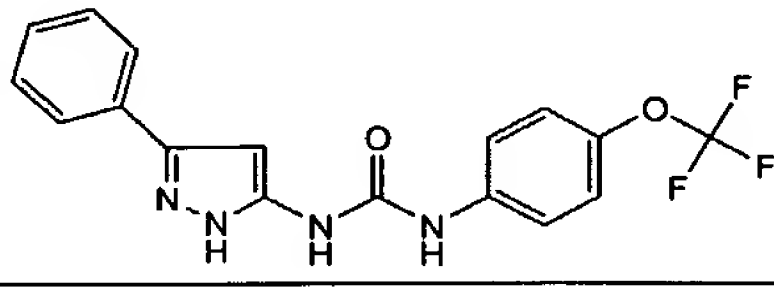
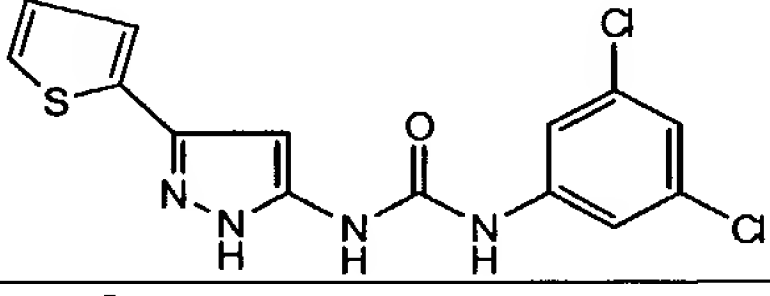
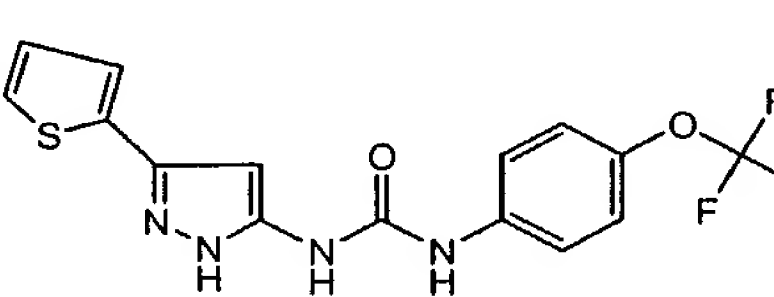
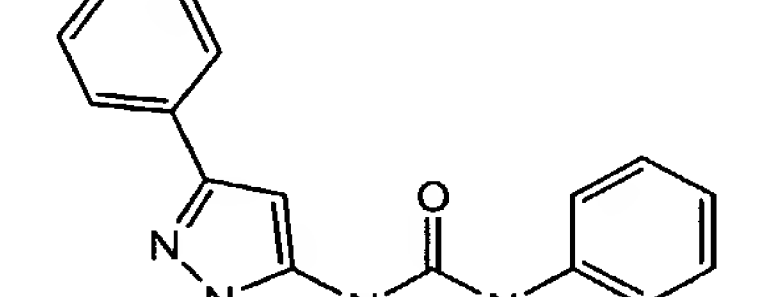
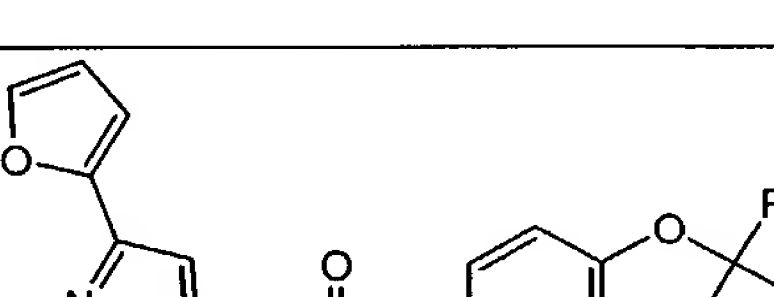
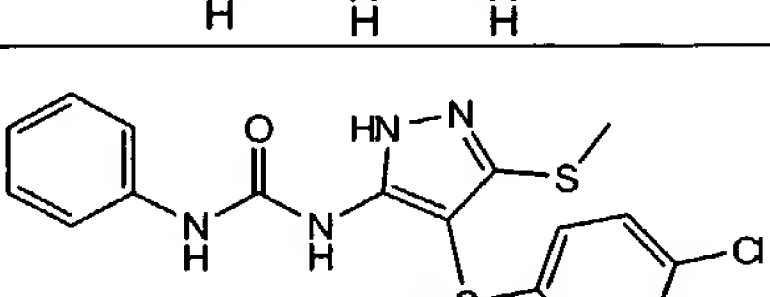
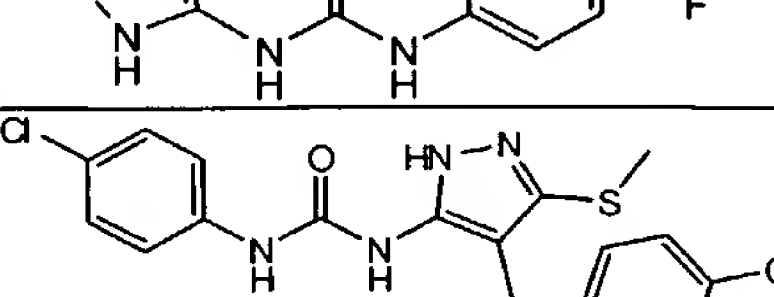
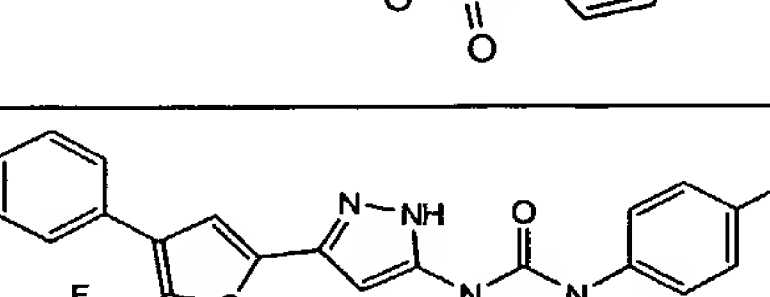
Table W

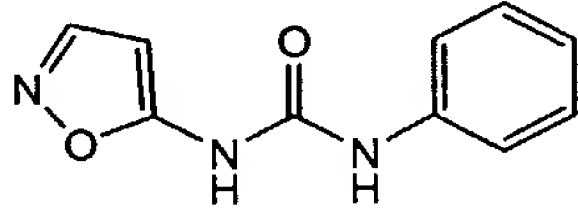
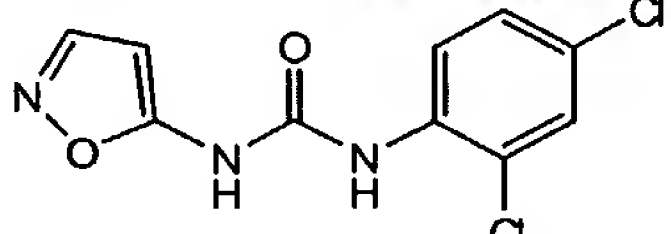
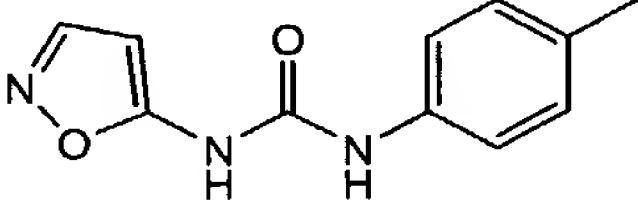
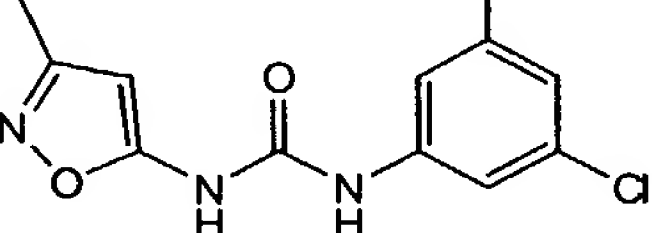
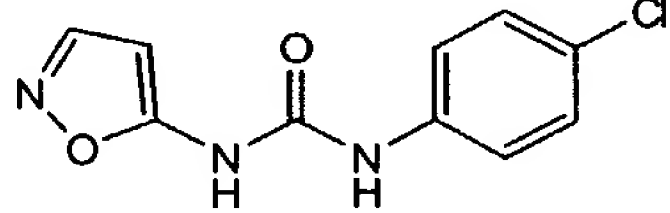
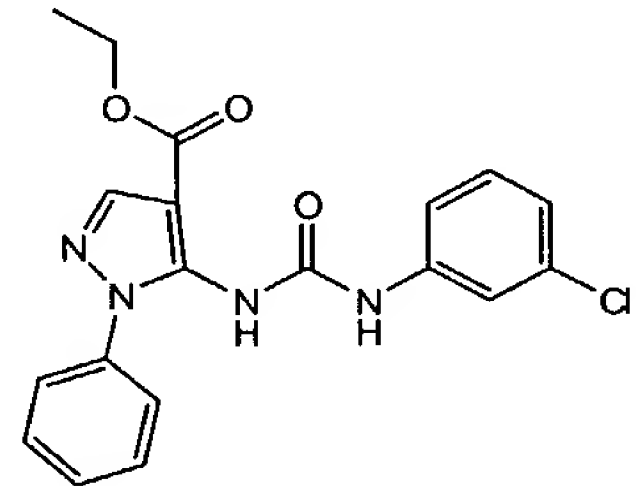
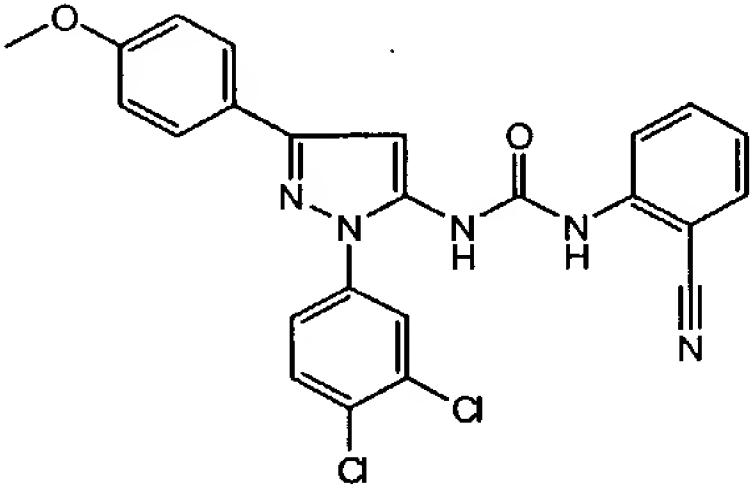
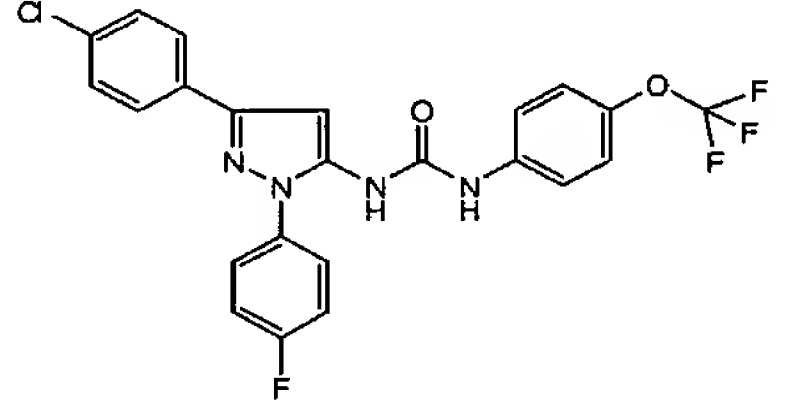
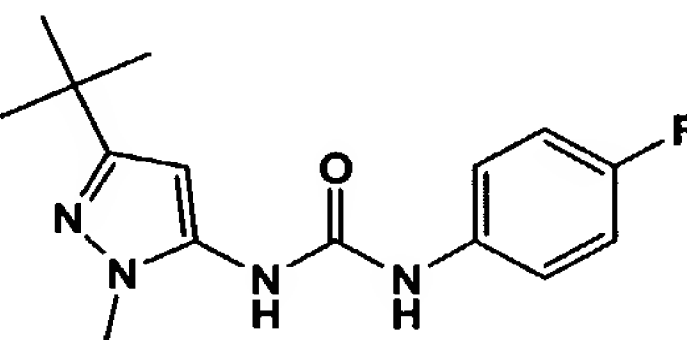
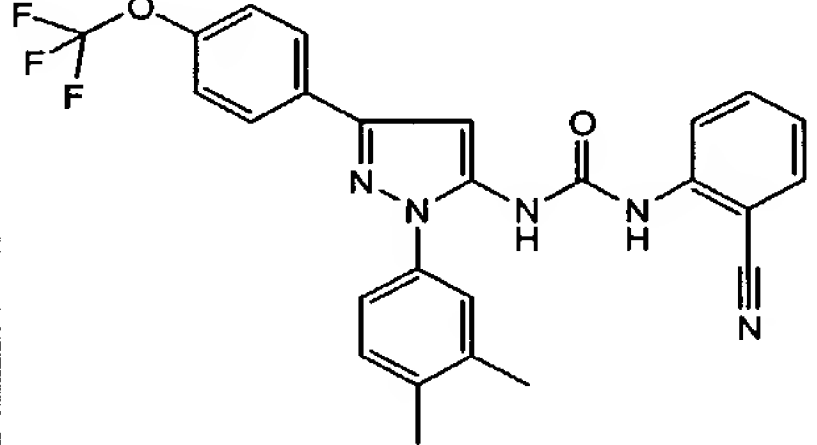
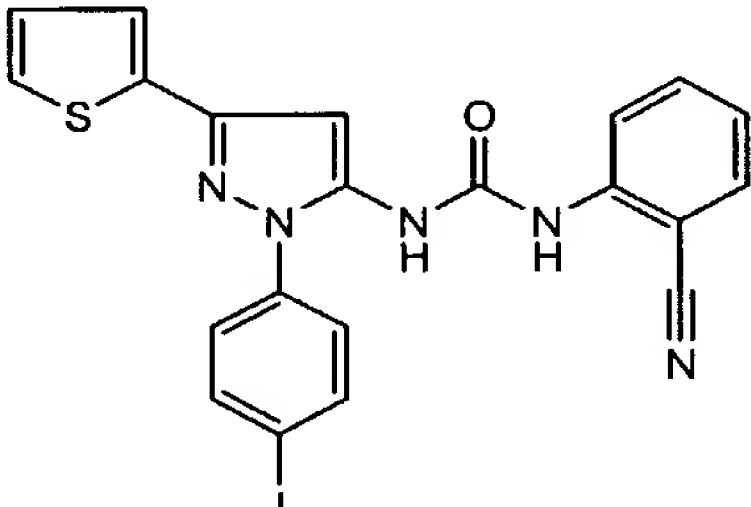
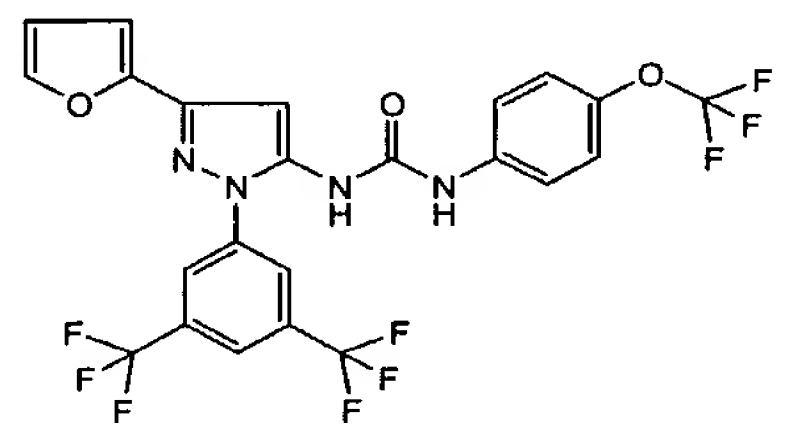
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
W1		W2	

Example Z: Commercially Available Ureas

Compounds Z1-Z93 as shown in Table Z are commercially available:

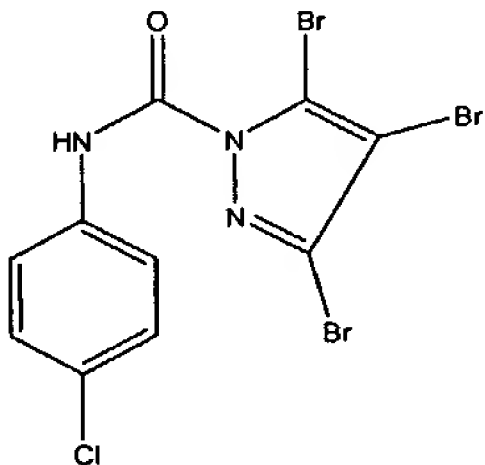
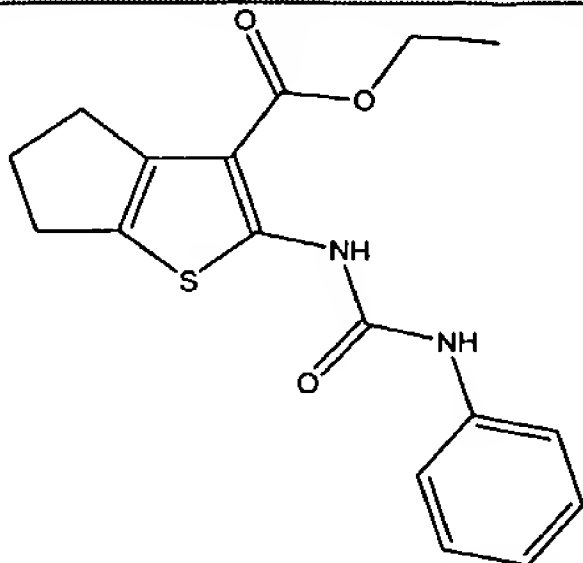
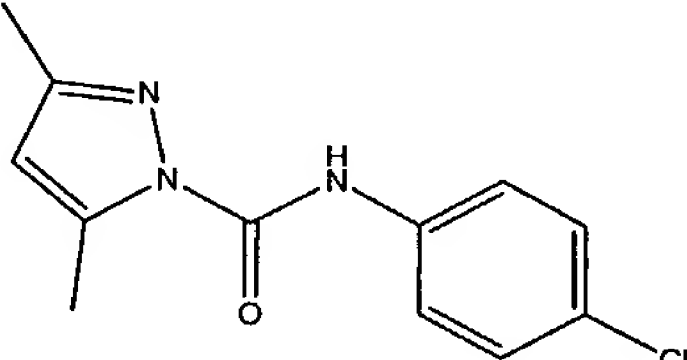
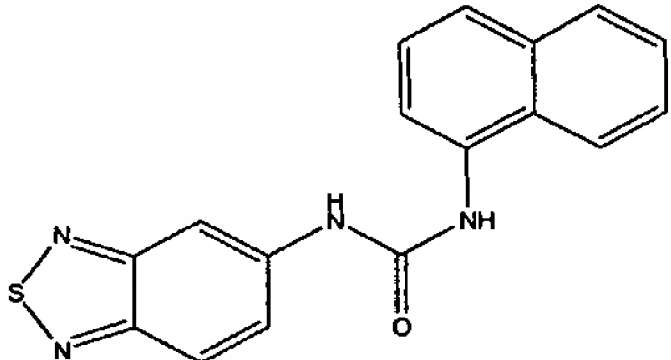
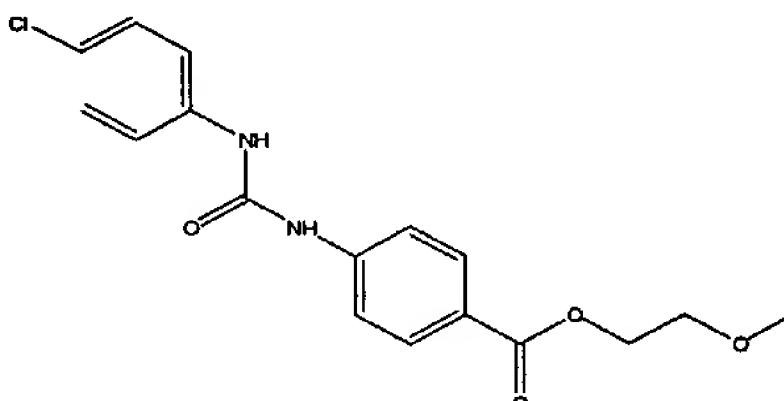
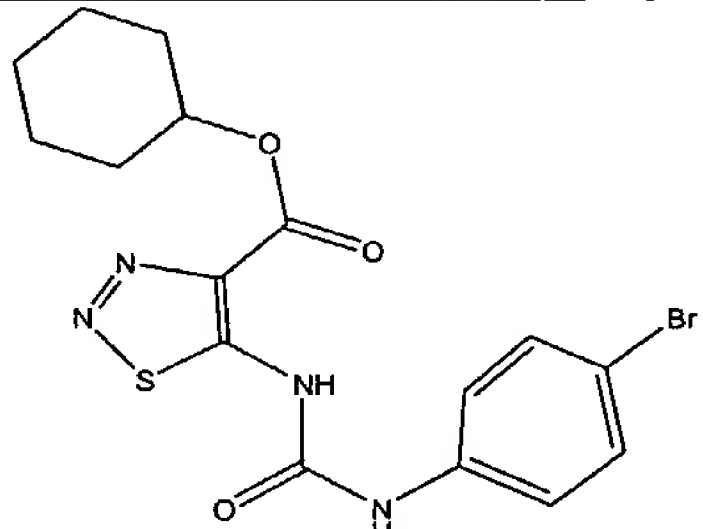
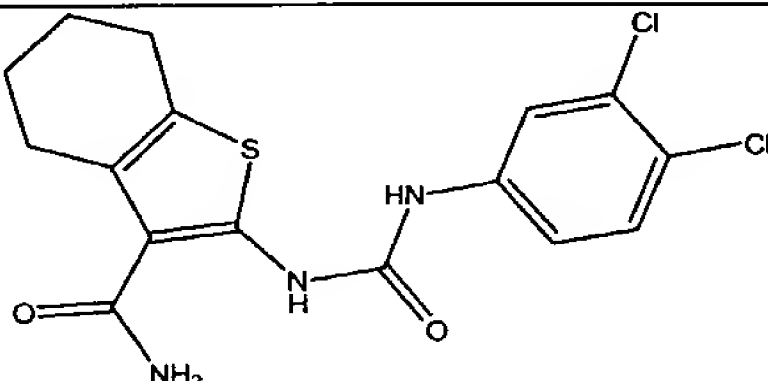
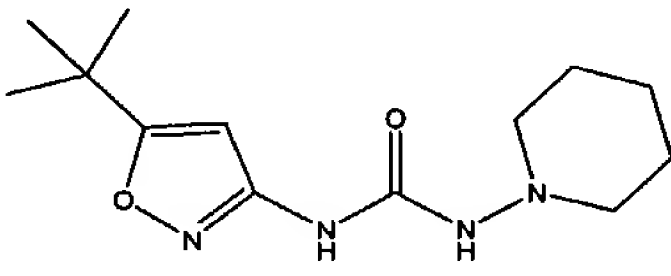
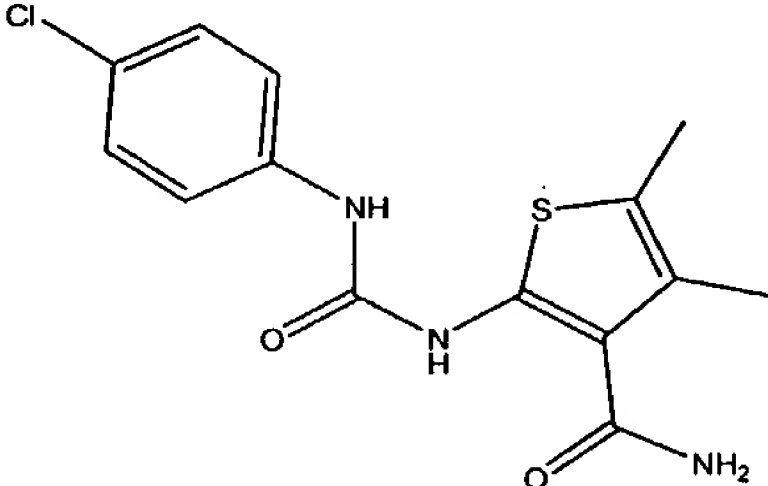
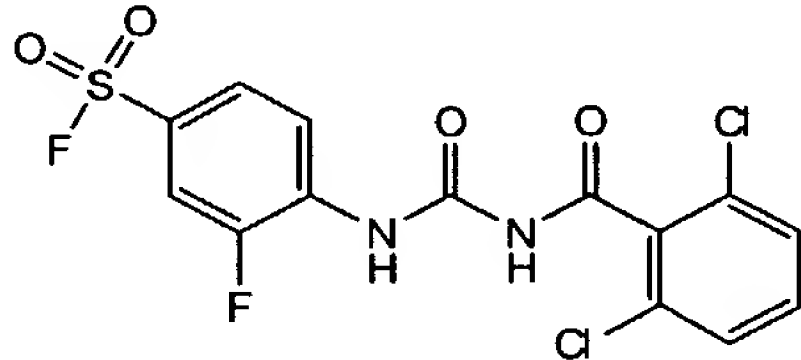
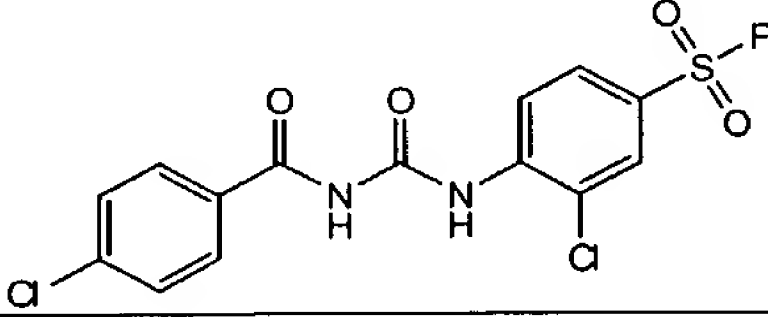
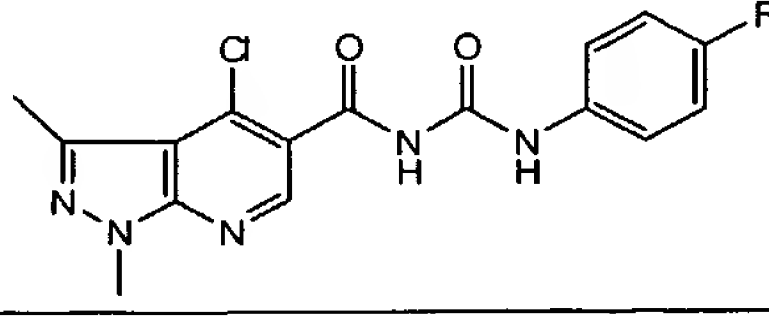
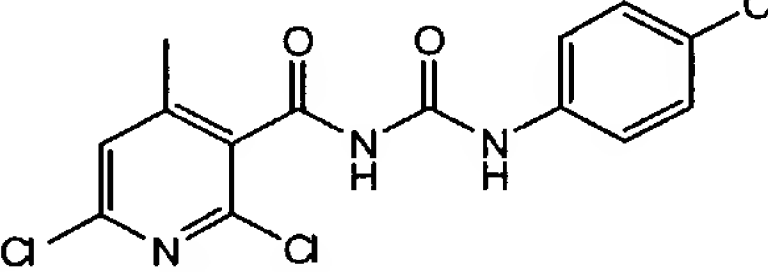
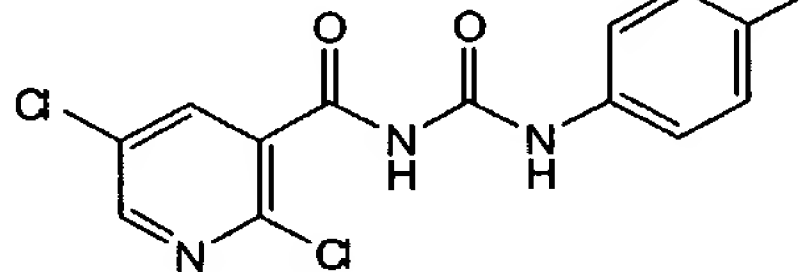
Table Z

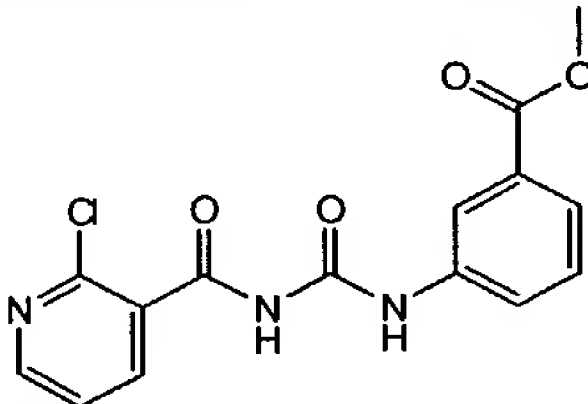
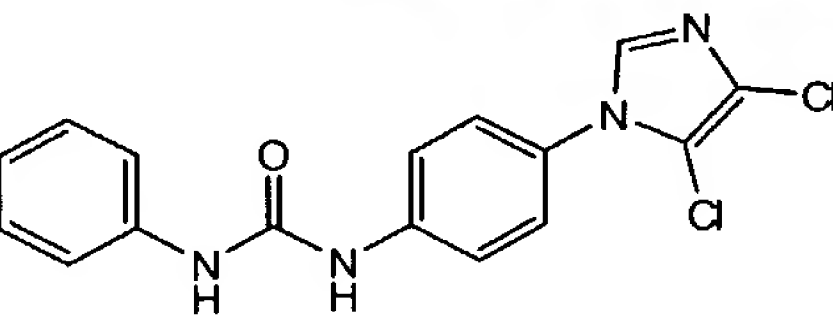
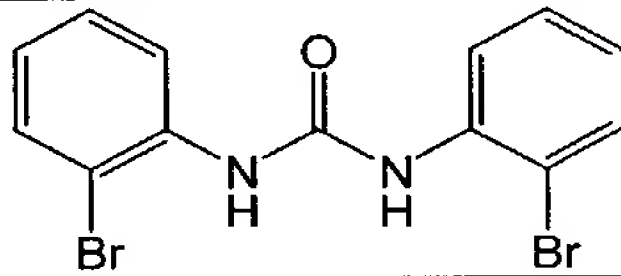
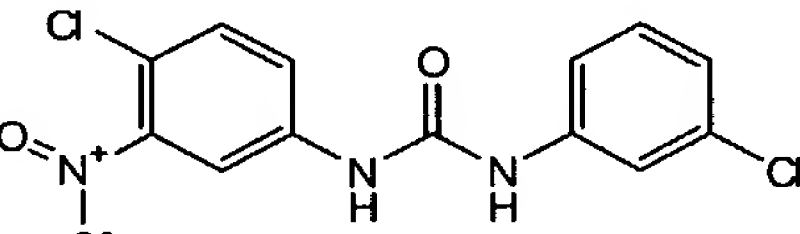
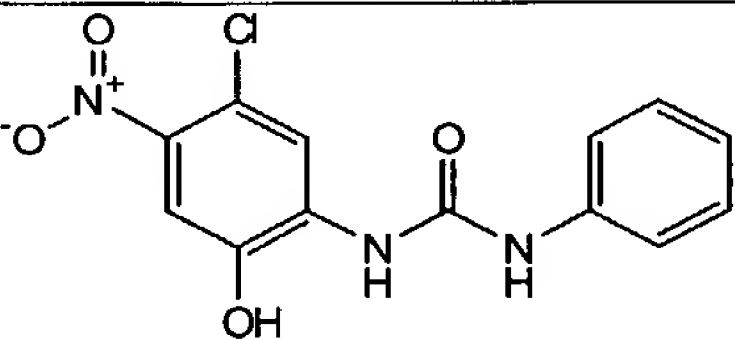
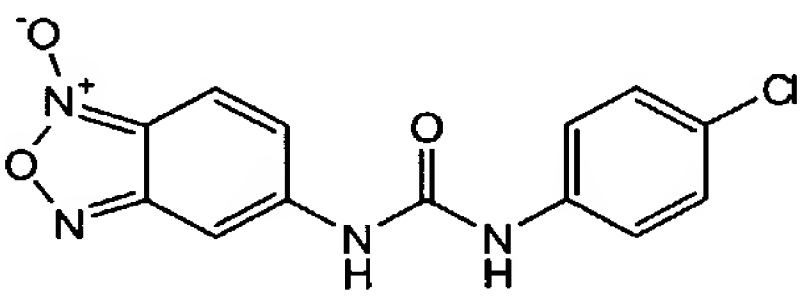
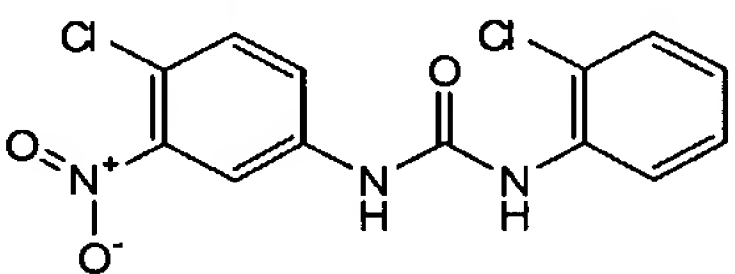
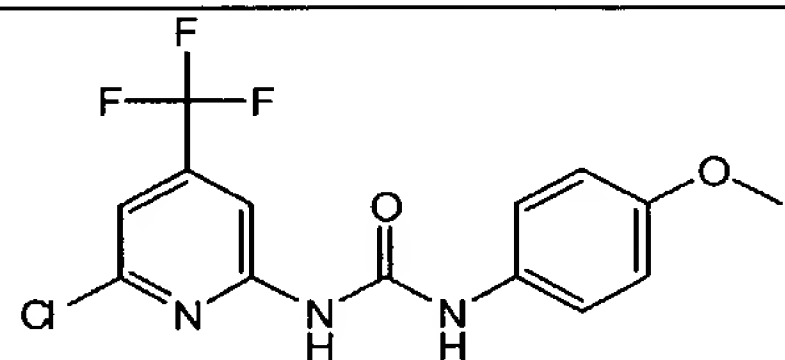
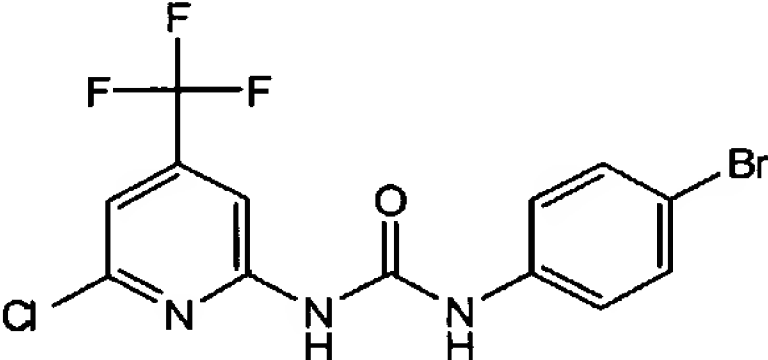
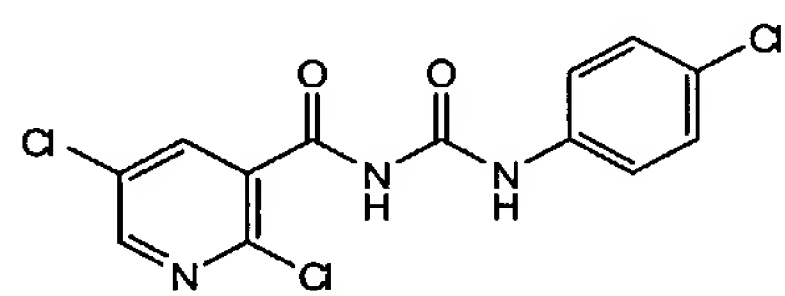
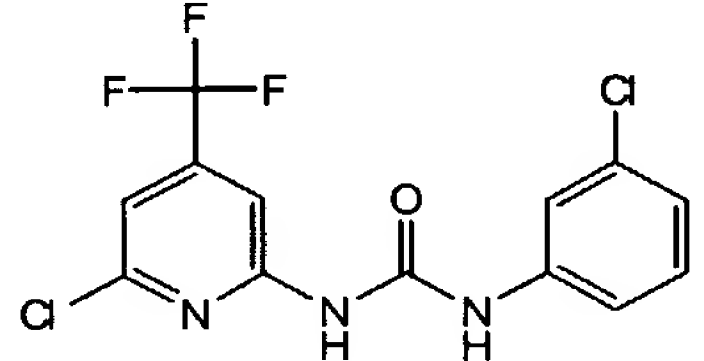
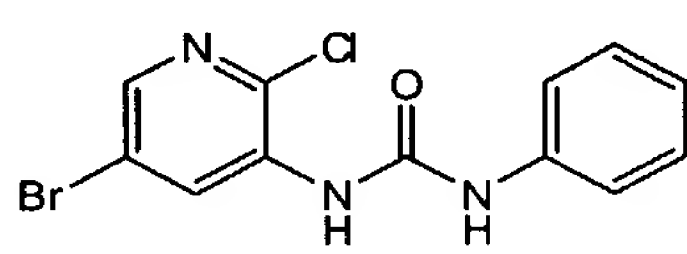
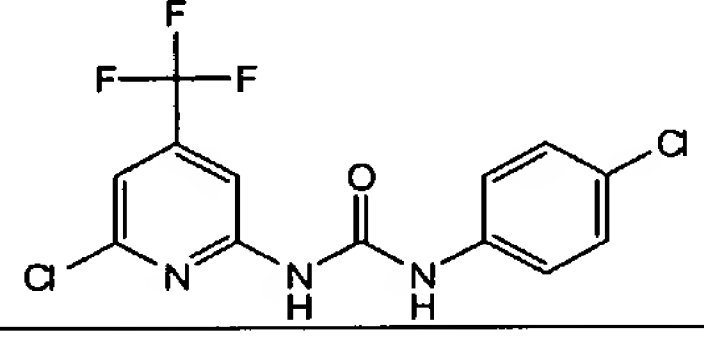
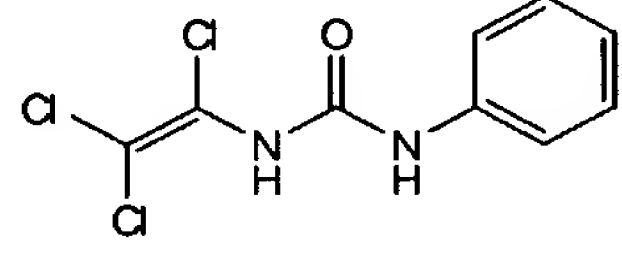
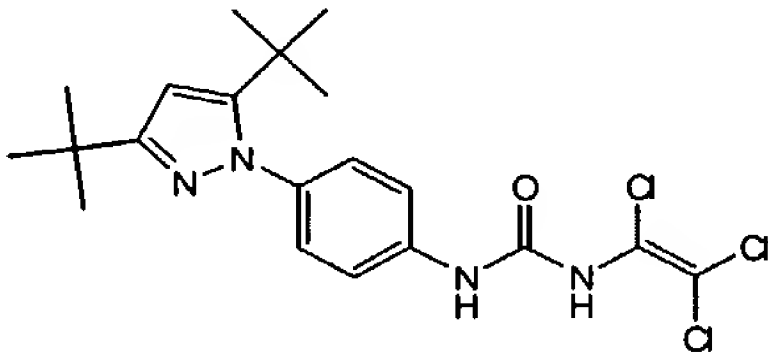
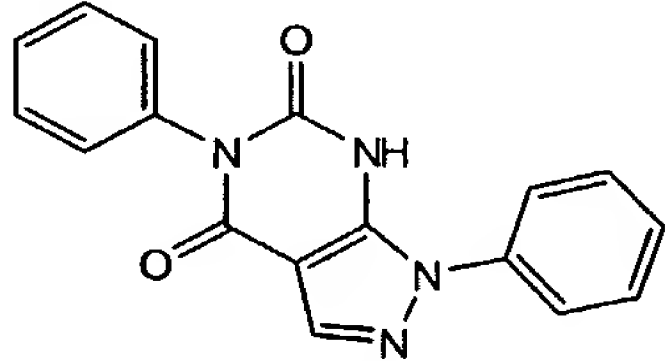
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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Z3		Z4	
Z5		Z6	
Z7		Z8	
Z9		Z10	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
Z11		Z12	
Z13		Z14	
Z15		Z16	
Z17		Z18	
Z19		Z20	
Z21		Z22	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
Z23		Z24	
Z25		Z26	
Z27		Z28	
Z29		Z30	
Z31		Z32	
Z33		Z34	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
Z35		Z36	
Z38		Z39	
Z40		Z43	
Z44		Z45	
Z46		Z47	
Z48		Z49	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
Z50		Z51	
Z52		Z53	
Z54		Z55	
Z56		Z57	
Z58		Z59	
Z60		Z61	
Z62		Z63	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
Z64		Z65	
Z66		Z67	
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Z70		Z71	
Z72		Z73	
Z74		Z75	
Z76		Z77	
Z78		Z79	

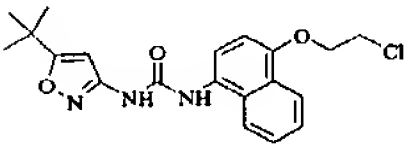
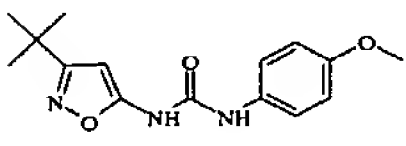
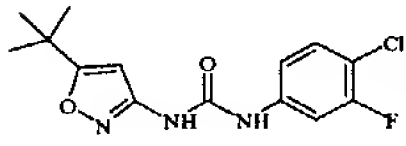
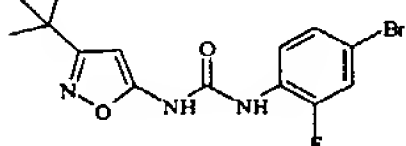
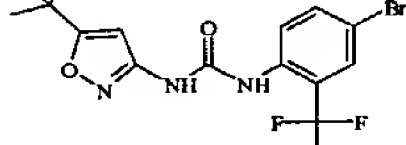
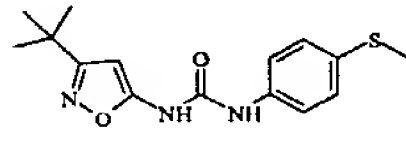
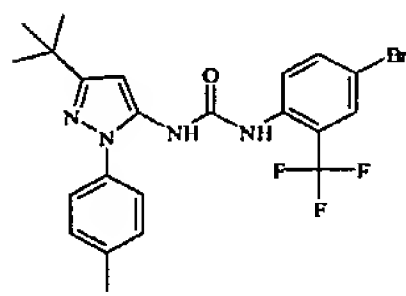
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
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Z86		Z87	
Z88		Z89	
Z90		Z91	
Z92		Z93	

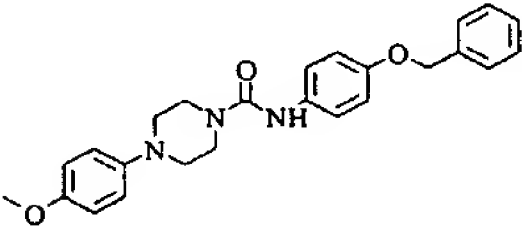
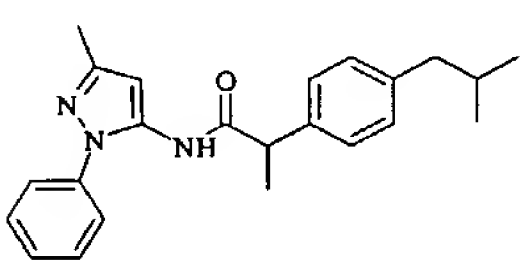
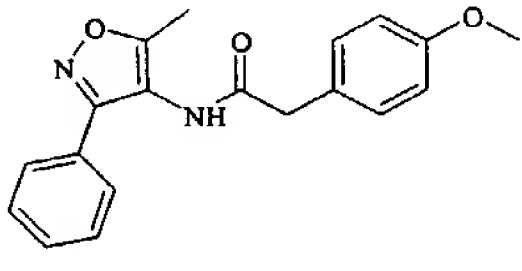
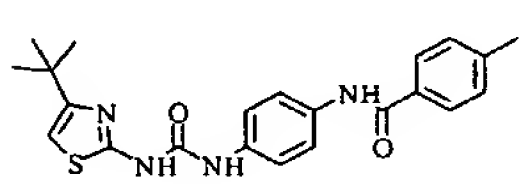
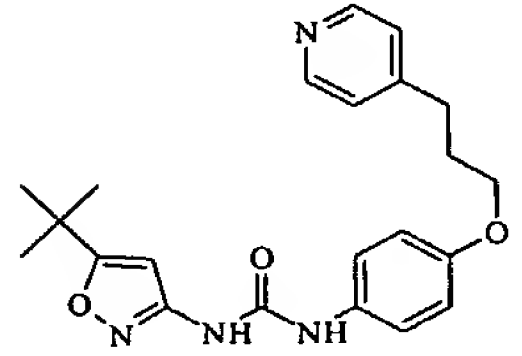
Binding Constant (K_d) Measurements for Small-Molecule- Kinase Interactions

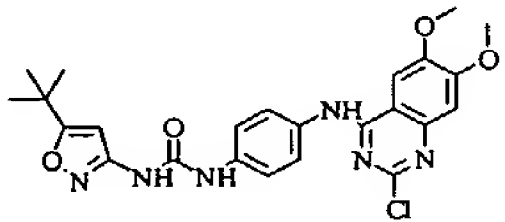
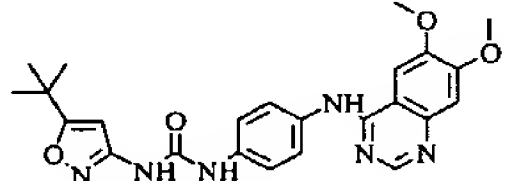
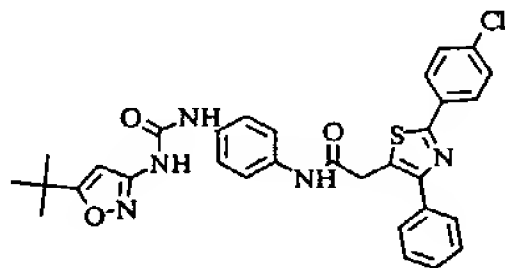
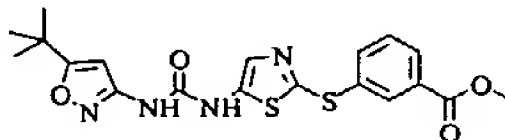
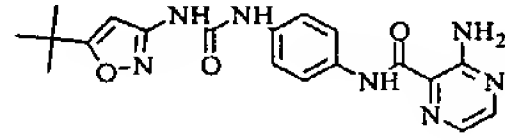
Methods for measuring binding affinities for interactions between small molecules and kinases including FLT3, c-KIT, p38, STK-10, MKNK2, ABL(T334I) [a.k.a. ABL(T315I)], VEGFR2 (a.k.a. KDR), and EGFR are described in detail in US Application No. 10/873,835, which is incorporated by reference herein in its entirety. The components of the assays include human kinases expressed as fusions to T7 bacteriophage particles and immobilized ligands that bind to the ATP site of the kinases. For the assay, phage-displayed kinases and immobilized ATP site ligands are combined with the compound to be tested. If the test compound binds the kinase it competes with the immobilized ligand and prevents binding to the solid support. If the compound does not bind the kinase, phage-displayed proteins are free to bind to the solid support through the interaction between the kinase and the immobilized ligand. The results are read out by quantitating the amount of fusion protein bound to the solid support, which is accomplished by either traditional phage plaque assays or by quantitative PCR (qPCR) using the phage genome as a template. To determine the affinity of the interactions between a test molecule and a kinase, the amount of phage-displayed kinase bound to the solid support is quantitated as a function of test compound concentration. The concentration of test molecule that reduces the number of phage bound to the solid support by 50% is equal to the K_d for the interaction between the kinase and the test molecule. Typically, data are collected for twelve concentrations of test compound and, the resultant binding curve is fit to a non-cooperative binding isotherm to calculate K_d .

Described in the exemplary assays below is data from binding with varying kinases. Binding values are reported as follows "+" for representative compounds exhibiting a binding dissociation constant (K_d) of 10,000 nM or higher; "++" for representative compounds exhibiting a K_d of 1,000 nM to 10,000 nM; "+++" for representative compounds exhibiting a K_d of 100 nM to 1,000 nM; and "++++" for representative compounds exhibiting a K_d of less than 100 nM. The term "ND" represents non-determined values.

Binding Constant (K_d) Measurements for Small-Molecule-Abl Interactions

Structure	Binding Assay:AB L1(DKIN): Kd (nM)
	+
	+
	+
	+
	+
	+
	+

Structure	Binding Assay:AB L1(DKIN): Kd (nM)	Binding Assay:AB L1(E274K):Kd (nM)	Binding Assay:AB L1(E255K):Kd (nM)	Binding Assay:AB L1(T315I): Kd (nM)
	+	ND	ND	ND
	ND	+	ND	ND
	ND	ND	+	++
	ND	ND	+	+
	ND	ND	+	ND

CompoundID	Structure	Binding Assay:AB L1(DKIN):Kd (nM)	Binding Assay:AB L1(E274K):Kd (nM)	Binding Assay:AB L1(E255K):Kd (nM)	Binding Assay:AB L1(T315I):Kd (nM)	Binding Assay:AB L1(H396P):Kd (nM)	Binding Assay:AB L1(Y253F):Kd (nM)	Binding Assay:AB L1(Q252H):Kd (nM)
AB200465		++	ND	+	++	+	+	++
AB200515		++++	ND	+++	++++	+++	+++	+++
AB200519		+++	ND	ND	ND	ND	ND	ND
AB200542		ND	ND	ND	+++	ND	ND	ND
AB200553		ND	+	ND	ND	ND	ND	ND

The Affinity of the Compounds for FLT3

The ability of FLT3 kinase inhibitors to inhibit cellular proliferation was also examined. MV4:11 was a cell line derived from a patient with acute myelogenous leukemia. It expressed a mutant FLT3 protein that was constitutively active. MV4:11 cells were grown in the presence of candidate FLT3 inhibitor molecules, resulting in significantly decreased proliferation of the leukemia-derived cells in the presence of compound. Inhibition of FLT3 kinase activity prevented proliferation of these cells, and thus the MV4:11 cell line can be used a model for cellular activity of small molecule inhibitors of FLT3.

10 *FLT3 assay using MV4,11 cells*

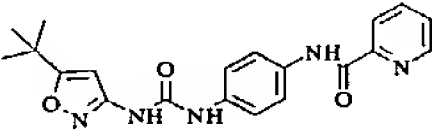
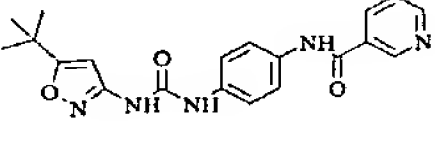
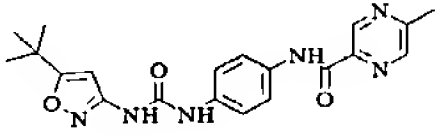
MV4,11 cells were grown in an incubator @ 37°C in 5% CO₂ in Medium 2 (RPMI, 10%FBS, 4mM glutamine, Penn/Strep). The cells were counted daily and the cell density was kept between 1e5 and 8e5 cells/ml.

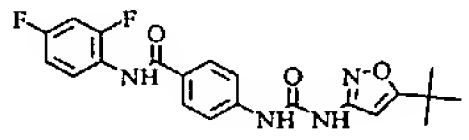
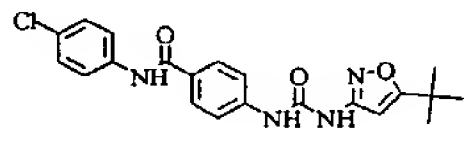
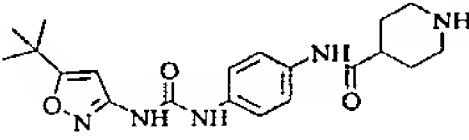

Day One: Enough cells were harvested for experiments to be conducted in 50ml conical tubes. The harvested cells were spun at 500g for 5 min at 4°C, the supernatant was then aspirated and the cells were resuspended in the starting volume of 1 x PBS. The cells were again spun at 500g for 5 min at 4°C and the supernatant again aspirated. The cells were then resuspended in medium 3 (DMEM w/ glut, 10% FBS, Penn/Strep) to a density of 4e5 cells/ml and incubated @ 37°C in 5% CO₂ O/N.

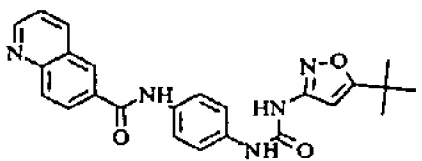
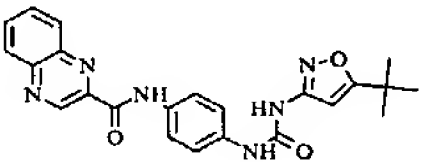
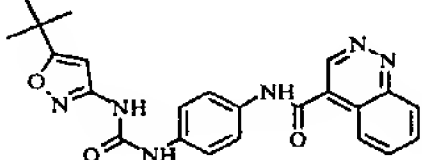
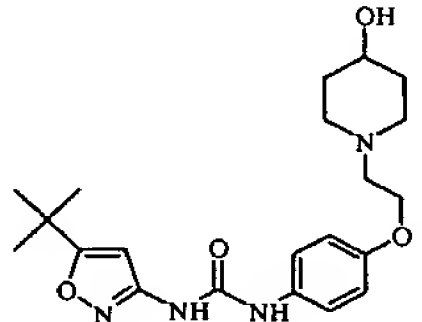
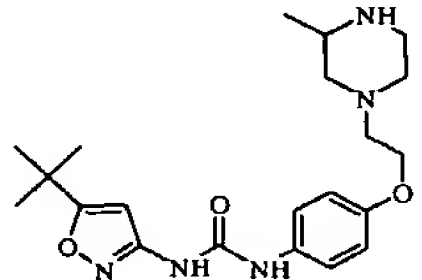
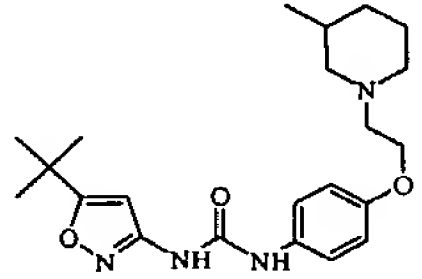
Day Two: The cells were counted and enough medium 3 was added to decrease density to 2e5 cells/ml. 50ul (10,000 cells) was aliquoted into each well of a 96 well optical plate using multichannel pipetman. The compound plate was then set up by aliquoting 3 µl of negative control (DMSO) into column 1 of a 96 well 300ul polypropylene plate, aliquoting 3 µl of positive control (10mM AB20121) into column 12 of plate, and aliquoting 3 µl of appropriate compounds from serial dilutions into columns 2-11. To each well, 150 µl of Medium 3 was added and 50 µl of compound/medium mixture from compound plate into rows of optical plate in duplicate. The cells were then incubated @ 37°C in 5% CO₂ for 3 days.

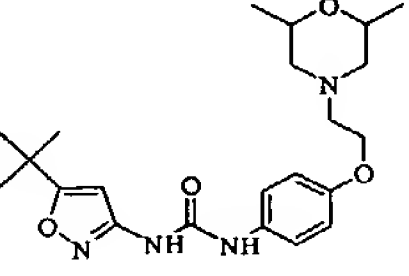
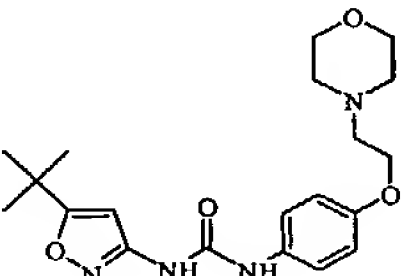
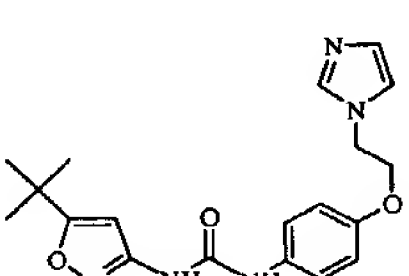
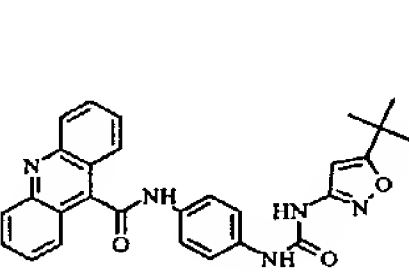
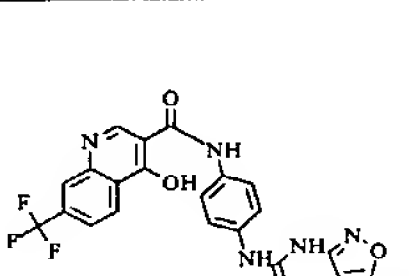
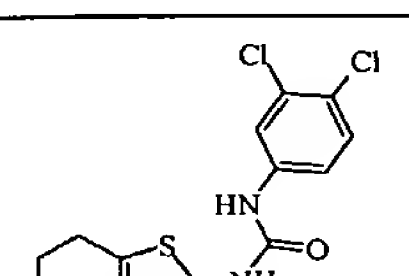
Day Five: MTS was thawed in a H₂O bath. 20 µl of MTS was added to each well of optical plate and the cells were incubated @ 37°C in 5% CO₂ for 2 hours. The plate was then placed on a plate shaker for 30 seconds on high speed.

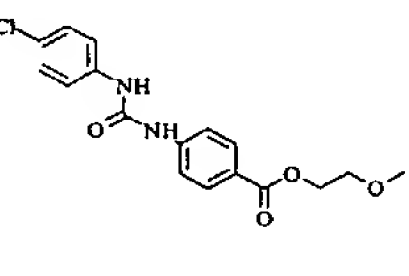
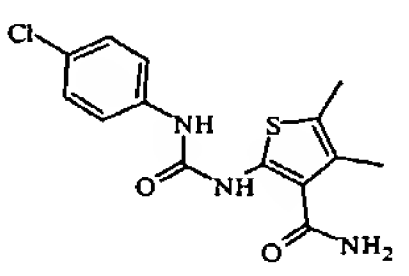
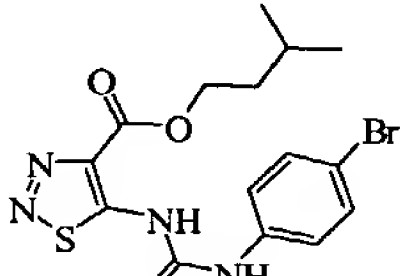
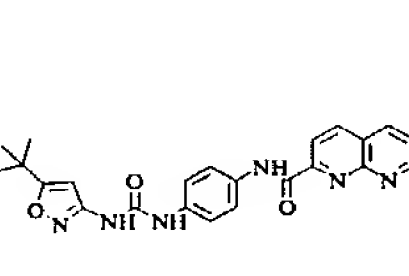
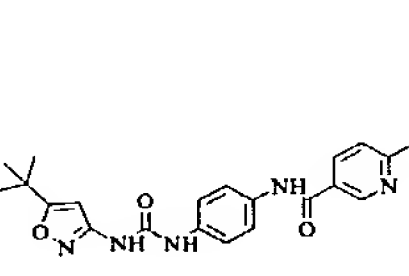
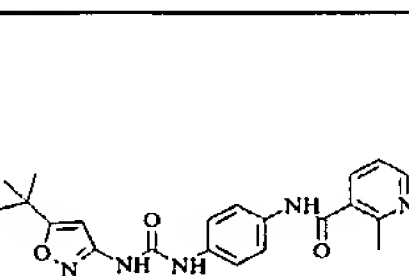
Data for some of the compounds is provided below:

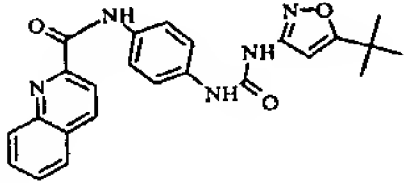
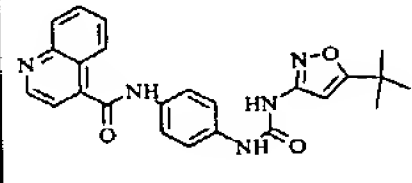
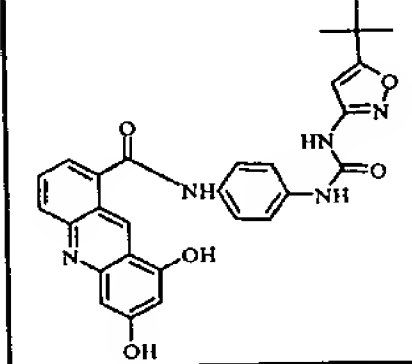
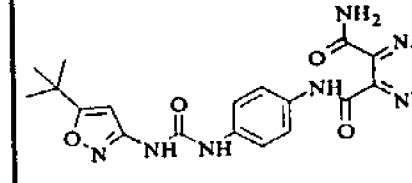
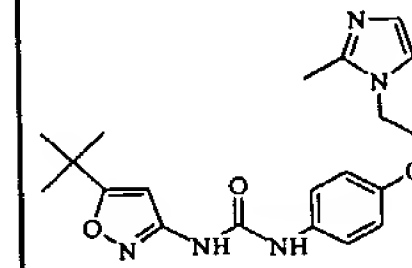
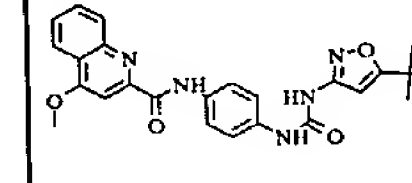
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminus):Kd (nM)	Binding Assay:FLT 3(JMplus): Kd (nM)
	++++	++++	++++	+	++++	+++
	++++	+++	ND	ND	ND	ND
	++++	++++	++++	+	ND	ND

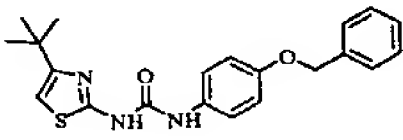
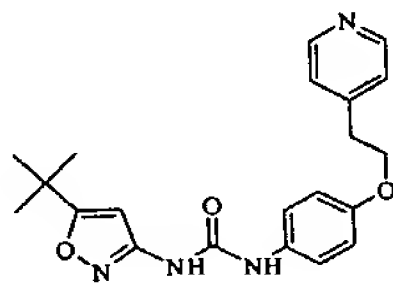
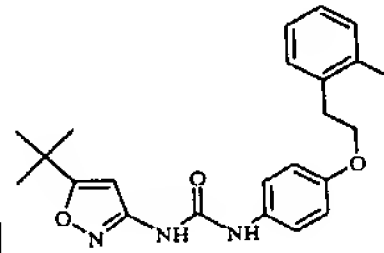
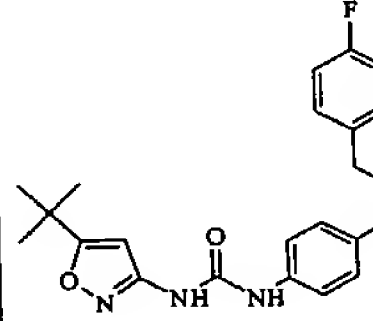
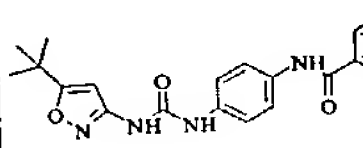
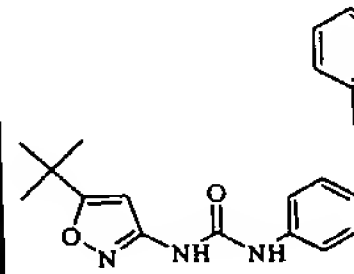
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)
	++++	+++
	++++	+++
	+++	+
	+++	++

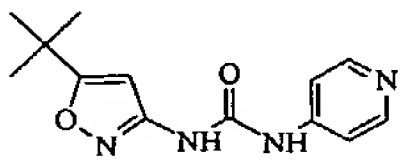
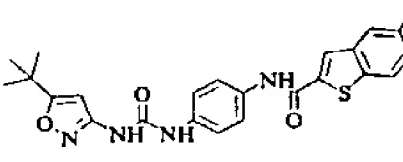
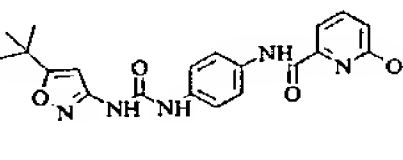
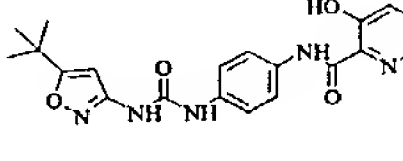
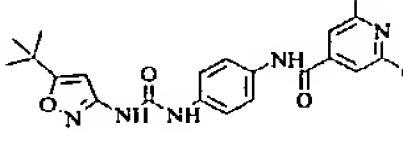
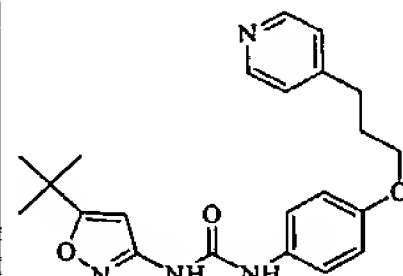
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	++++	+
	+++	++	ND	ND
	++++	++++	++++	++
	+++	++	ND	ND
	++	++	ND	ND
	++	++	ND	ND

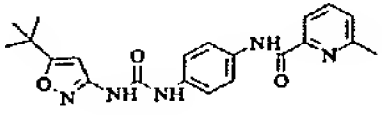
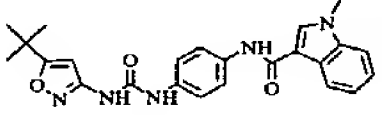
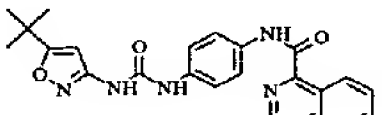

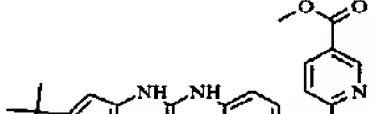
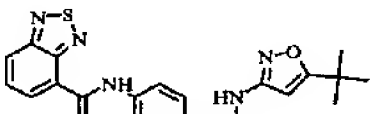

Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)	Cell Assay:CS 0001:IC ₅₀ (nM)
	+++	++
	+++	++
	++++	+++
	+++	++
	+++	+++
	+	+++


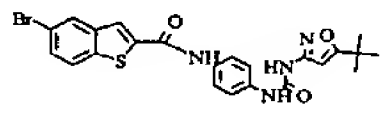
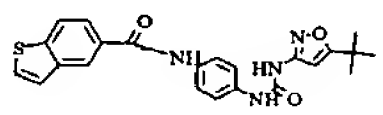
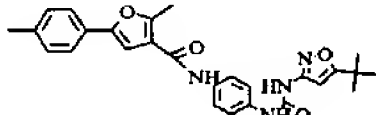
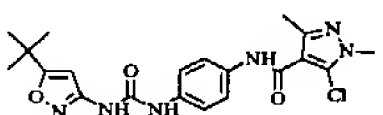
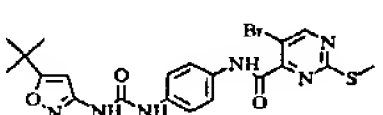
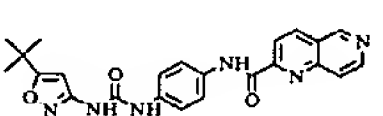
Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)	Cell Assay:CS 0001:IC ₅₀ (nM)
	++	++
	+	++
	+	++
	++++	+++
	++++	+++
	++++	+++

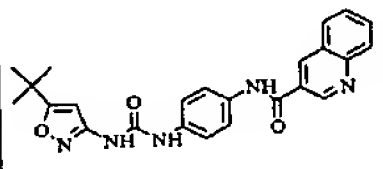
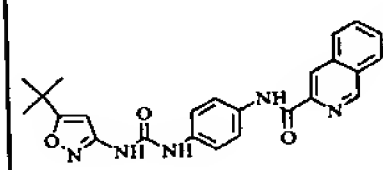
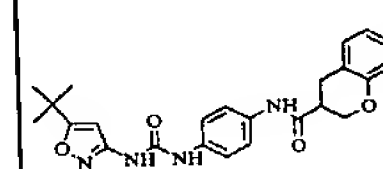
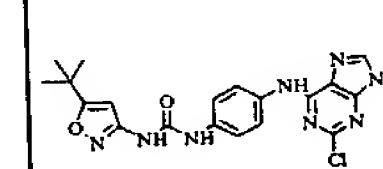
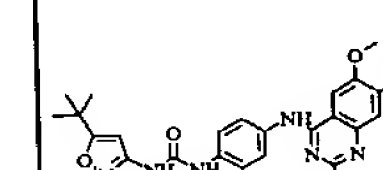
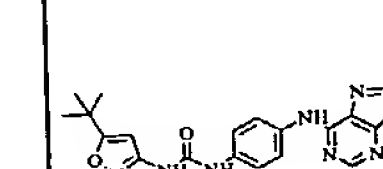
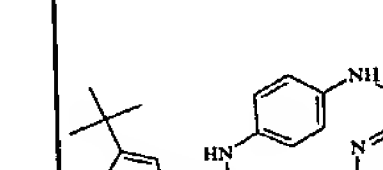
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	++++	++
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	+++	+++	ND	ND
	++++	++	ND	+
	++++	+++	ND	ND
	++++	++++	+++	++

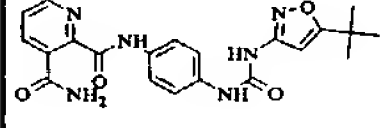
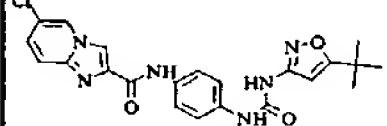
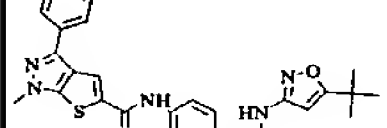
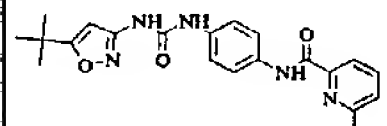
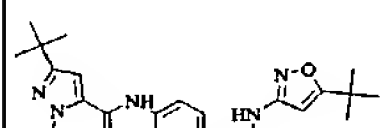
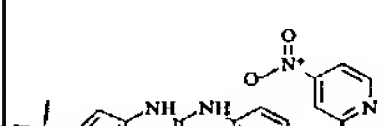
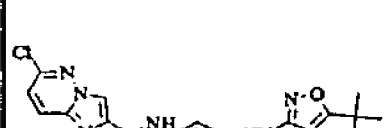
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++	+++	ND	ND
	++++	++++	++++	+
	++++	++++	+++	++
	++++	+++	ND	ND
	++++	++++	++++	+
	++++	+++	ND	ND

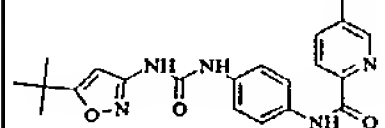
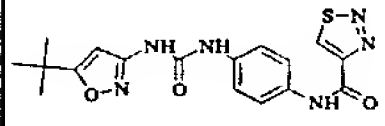

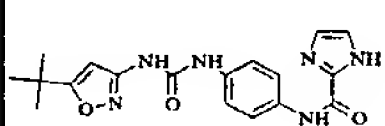
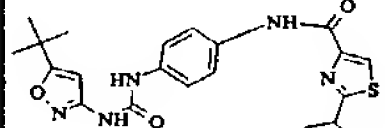
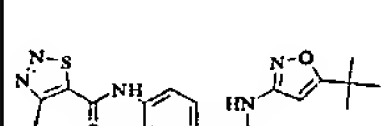
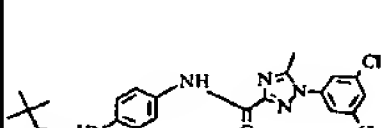
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminus):Kd (nM)	Binding Assay:FLT 3(JMplus):Kd (nM)
	++	++	ND	ND	ND	ND
	++++	++++	++++	++	ND	ND
	++++	++++	+++	+	ND	ND
	++++	++++	++++	++	++++	+++
	+++	+++	ND	ND	ND	ND
	++++	++++	++++	+	ND	ND

Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	++++	++
	++++	++++	++++	++
	++++	++++	ND	ND
	++++	++++	++++	+++
	++++	++++	++++	+
	++++	++++	+++	+
	++++	+++	ND	ND

Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	++++	+
	++++	++++	++++	+++
	++++	++++	++++	+
	++++	+++	ND	ND
	++++	++++	++++	++
	++++	++++	+++	++
	++++	++++	++++	++

Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminus):Kd (nM)	Binding Assay:FLT 3(JMplus):Kd (nM)
	++++	++++	++++	++	ND	ND
	++++	++++	++++	+	++++	+++
	++++	+++	ND	ND	ND	ND
	++++	++++	++++	++	ND	ND
	++++	++++	++++	++	ND	ND
	++++	++++	++++	++	ND	ND
	++++	++++	++++	++	ND	ND

Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	+++	++	ND	ND
	++++	++++	++++	++
	++++	++++	++++	+++
	++++	++++	++++	+
	++++	+++	+++	ND
	++++	++++	++++	+
	++++	++++	++++	++

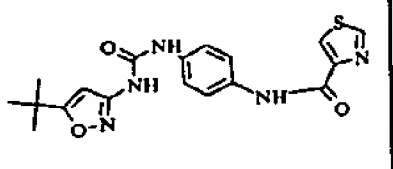
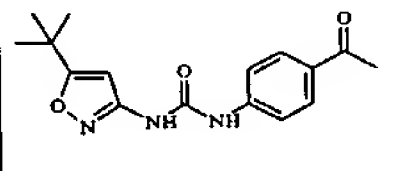
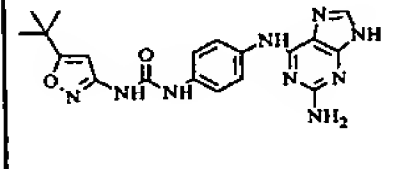
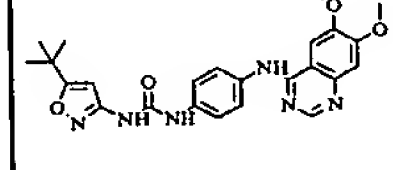
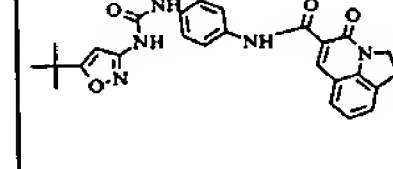
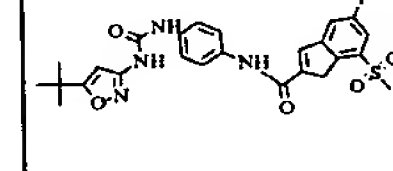
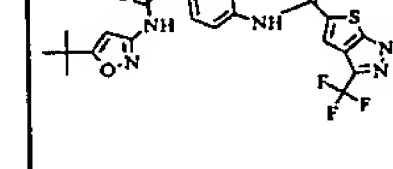
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	+++	ND	ND
	++++	+++	ND	ND
	++	++	ND	ND
	++++	++++	ND	ND
	++++	++++	+++	+
	+++	++	ND	ND
	+++	++	ND	ND

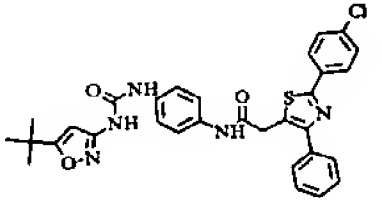
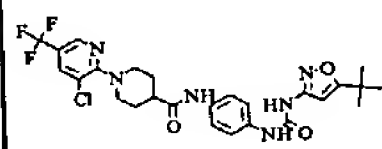
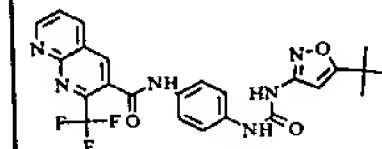
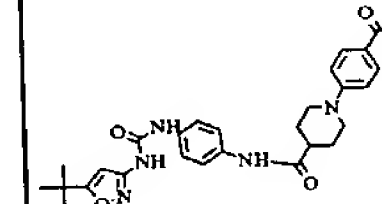
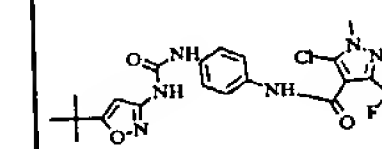
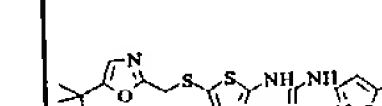
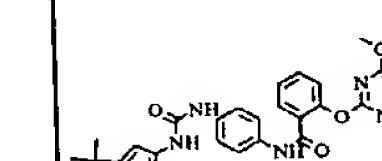
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	ND	++
	++	++	ND	ND
	++++	++++	+++	ND
	++++	+++	ND	ND
	++++	+++	ND	ND
	++++	+++	ND	ND
	+++	+++	ND	ND
	++++	++++	+++	+

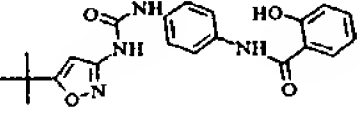
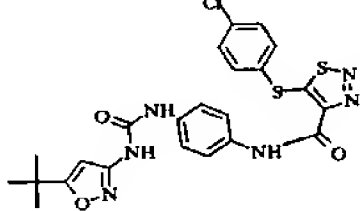
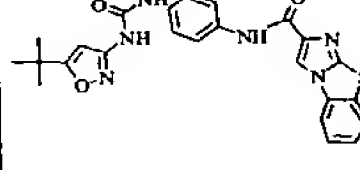
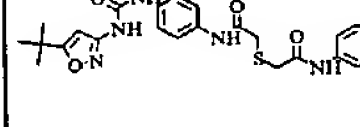
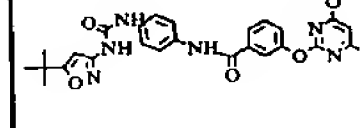
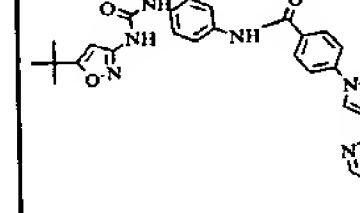
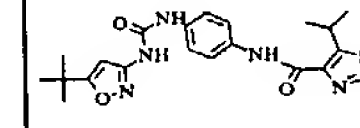
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	ND	ND
	++++	+++	ND	ND
	++++	++	ND	ND
	++++	++++	++++	+
	++++	++++	++++	++
	++++	++++	++++	+
	+++	++	ND	ND

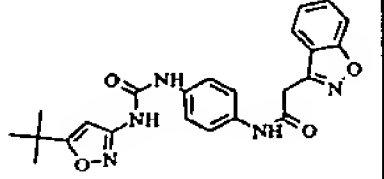
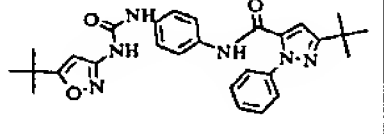
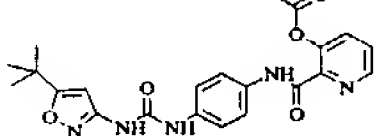
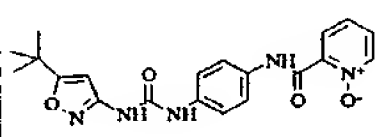
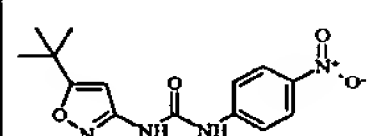

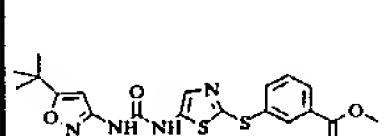
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++	++	ND	ND
	++++	+++	ND	ND
	++++	+++	ND	ND
	++++	+++	ND	ND
	++++	++++	ND	++
	++++	++++	+++	++
	++++	+++	ND	ND
	++++	+++	ND	ND

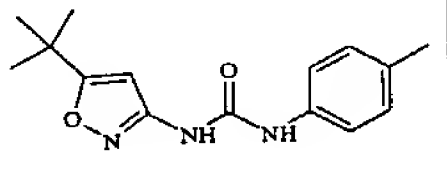
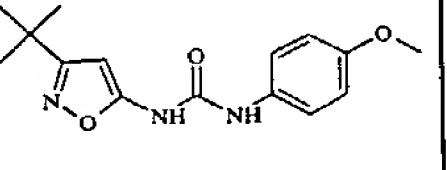
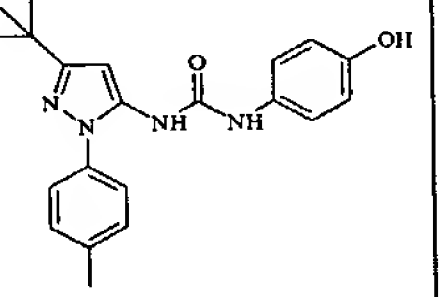
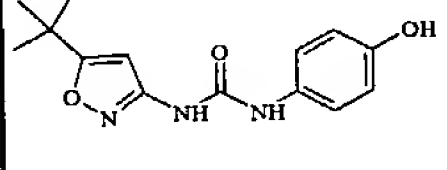
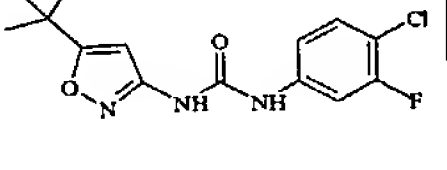
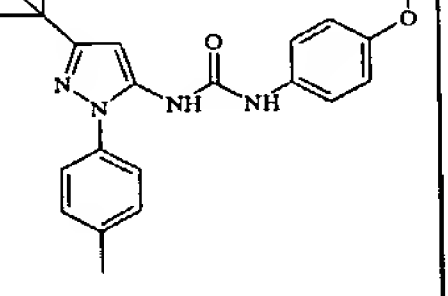
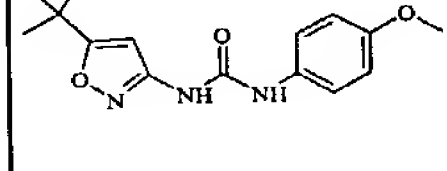
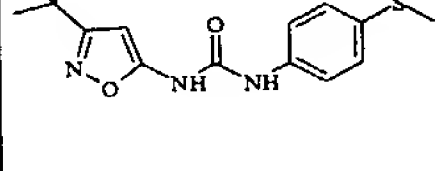
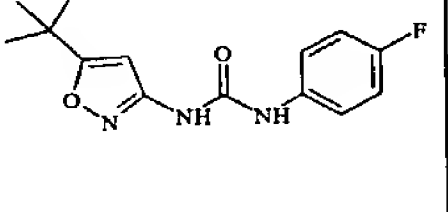
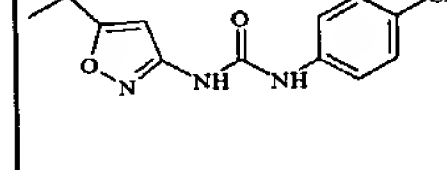
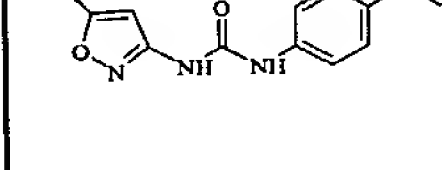
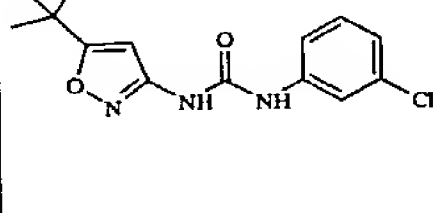
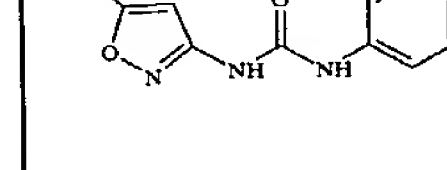
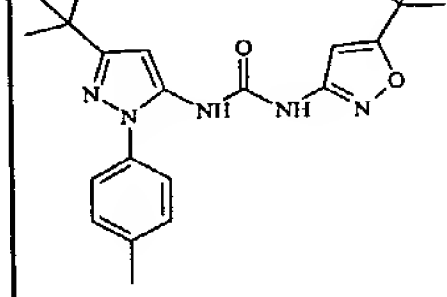
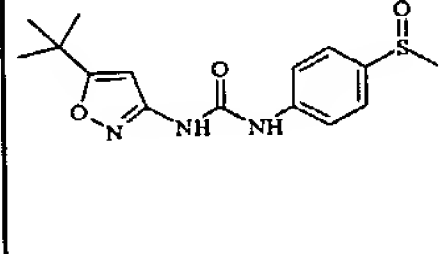
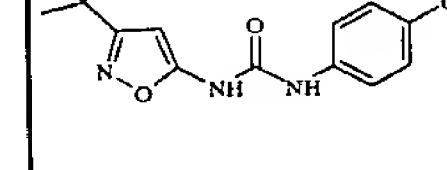
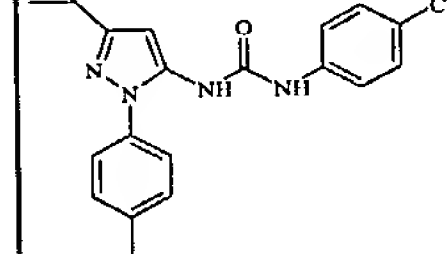
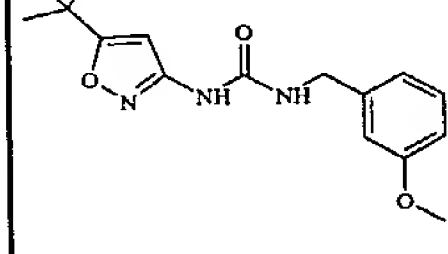
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	ND	+++
	++++	++++	++++	+++
	++++	++++	++++	++
	++++	+++	ND	++
	++++	+++	ND	ND
	+++	+++	ND	ND
	++++	+++	ND	ND

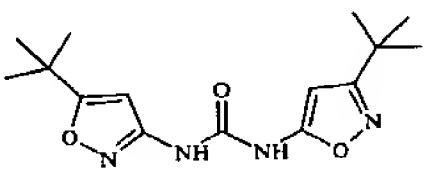
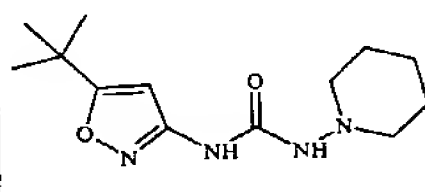
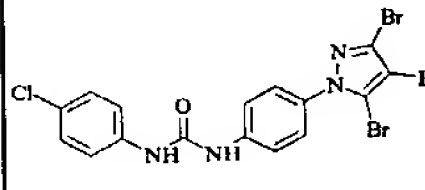
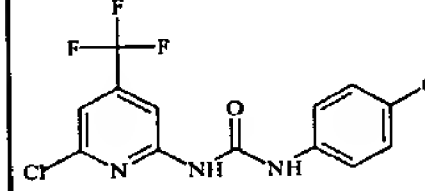
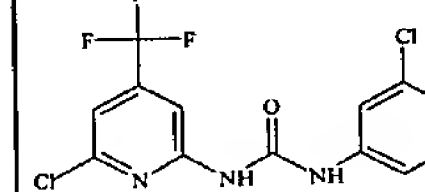
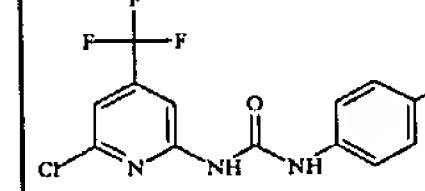
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	++++	+
	+++	+++	ND	ND
	++++	++++	++++	+
	++++	++++	++++	++
	++++	++++	++++	+
	++++	+++	ND	ND
	++++	+++	ND	+

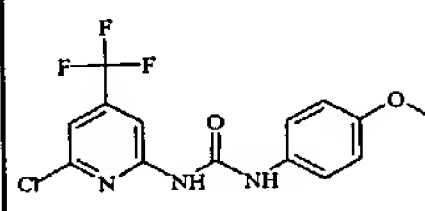
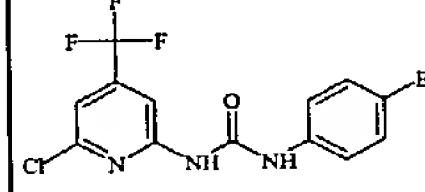
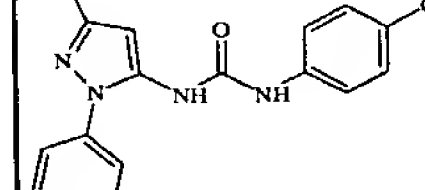
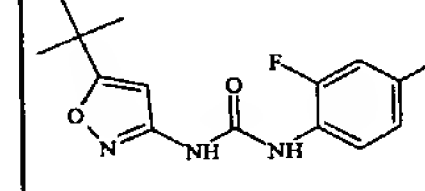
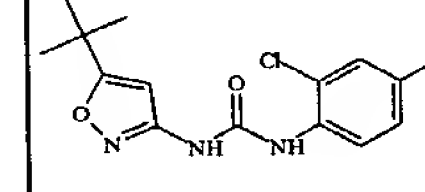
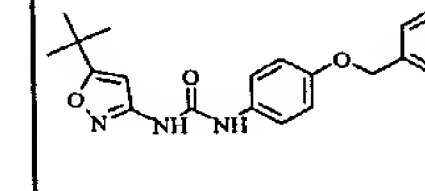
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminus):Kd (nM)
	++++	+++	ND	ND	ND
	+++	++++	ND	+	ND
	+++	+++	ND	ND	ND
	++++	++++	+++	+	ND
	++++	+++	ND	+++	ND
	ND	+++	ND	++	+++
	ND	++	ND	ND	+++

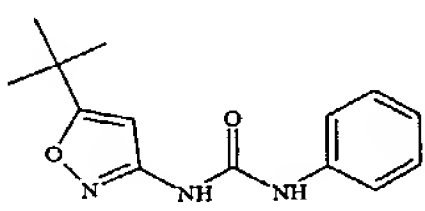
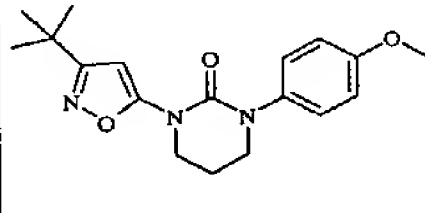
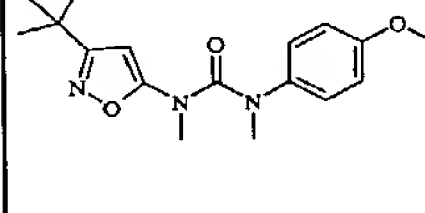
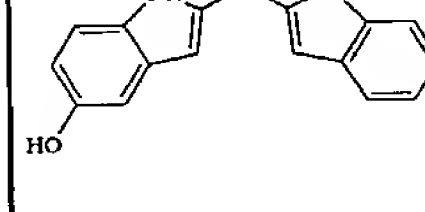
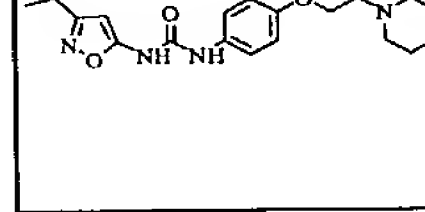
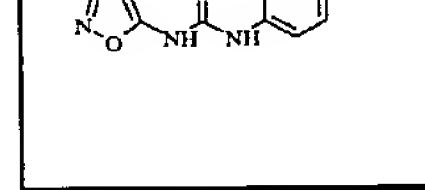
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminus):Kd (nM)
	ND	+++	ND	ND	++
	ND	++	ND	ND	+++
	ND	++++	++++	+++	++++
	ND	++++	++++	++	++++
	ND	++++	++++	++	++++
	ND	+++	ND	ND	+++
	ND	+	ND	++	++++

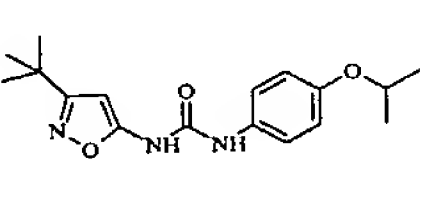
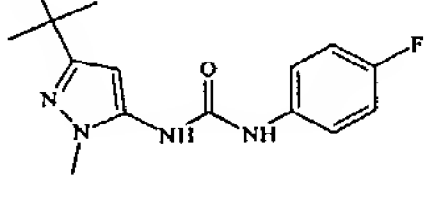
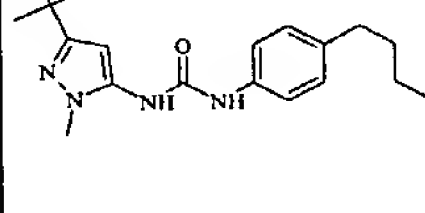
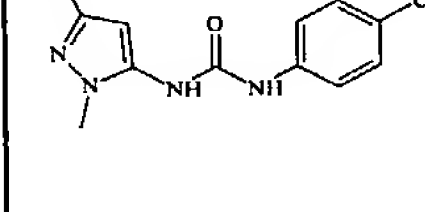
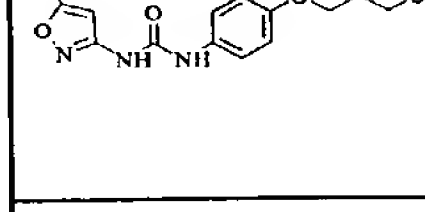
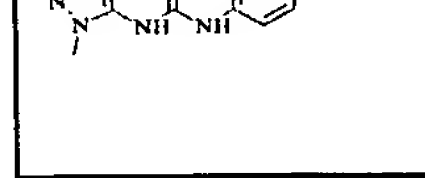
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminus):Kd (nM)
	ND	+++	ND	ND	+++
	ND	+++	ND	ND	+++
	ND	++++	++++	++	++++
	ND	++++	++++	+	++++
	ND	+++	ND	++	+++
	ND	+++	ND	++	+++
	ND	+++	ND	++	++++

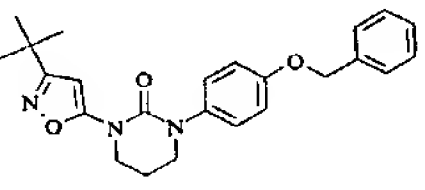
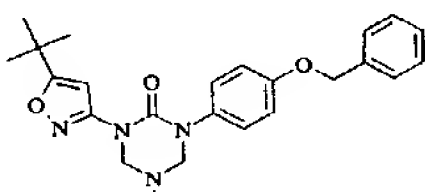
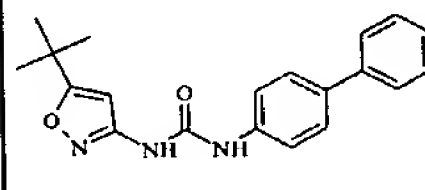
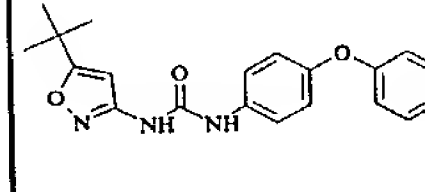
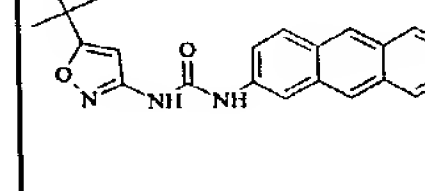
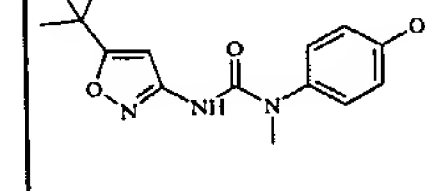
Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)	Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)	Cell Assay:CS 0001:IC ₅₀ (nM)	Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)
	+++++		+++++	+++		+++
	+++		+++	ND		+++++
	+++++		+++	ND		+++
	+++		+++++	ND		+++
	+++		+++++	ND		+++
	++++		+++++	ND		+++++

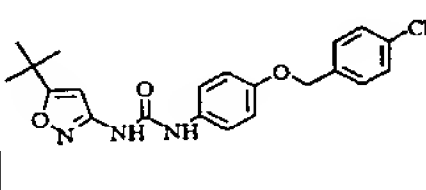
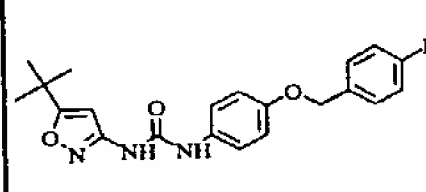
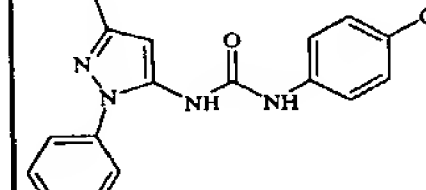
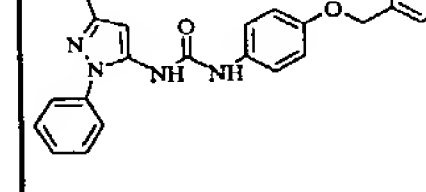
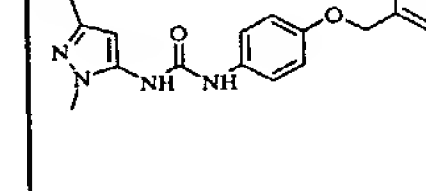
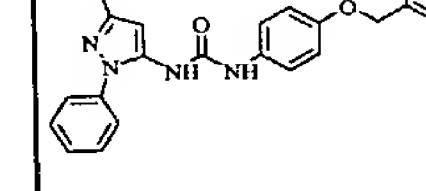
Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)
	++++
	++++
	++++
	++++
	++++
	+++++

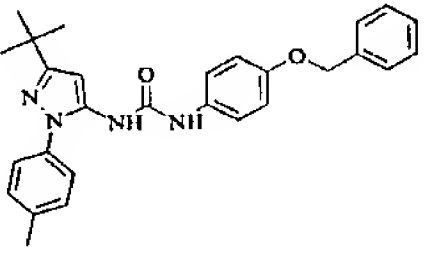
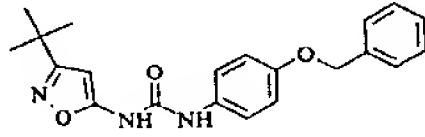
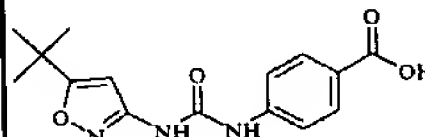
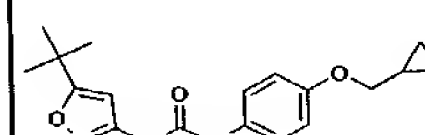
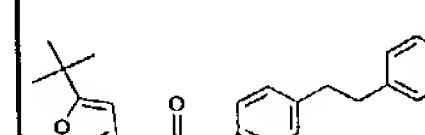
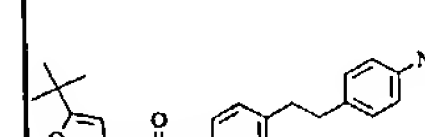
Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)	Cell Assay:CS 0001:IC ₅₀ (nM)	Cell Assay:CS 0005:IC ₅₀ (nM)
	+++++	+++	ND
	+++	ND	ND
	+++	ND	ND
	+++++	ND	ND
	+++	ND	ND
	+++++	+++++	+++

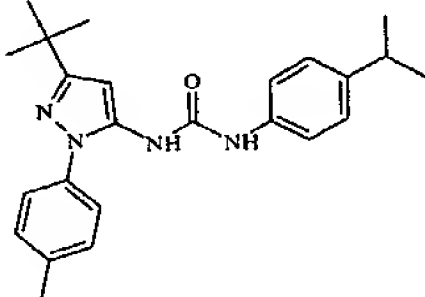
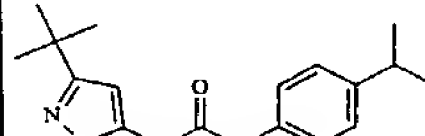
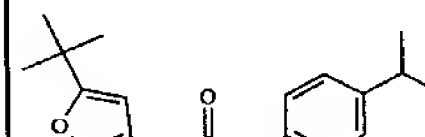
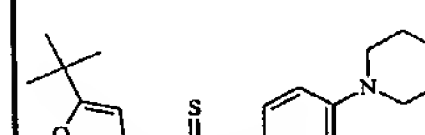
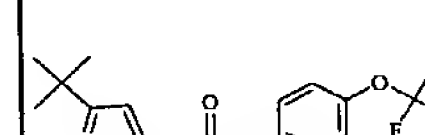
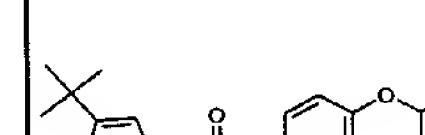
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)
	++++	ND
	++	ND
	+	ND
	++++	+++
	+++	ND
	++++	++++

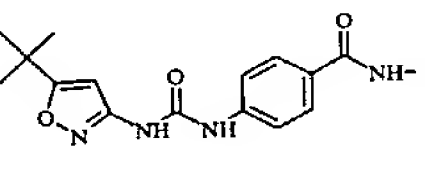
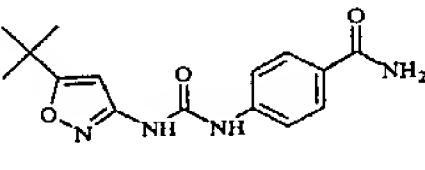
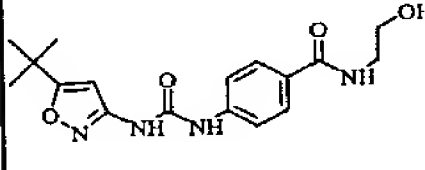
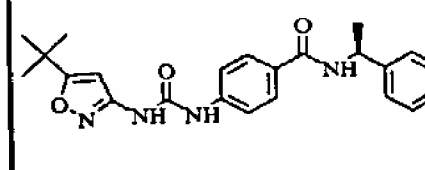
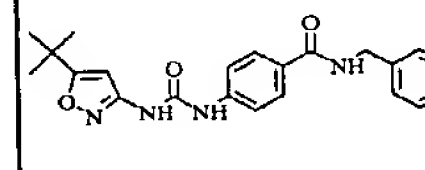
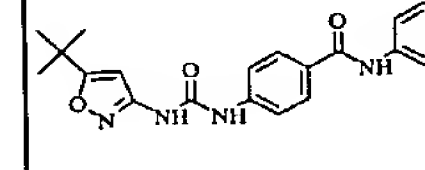
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)
	++++	+++
	+++	ND
	+++	ND
	+++	ND
	++++	ND
	++++	++++

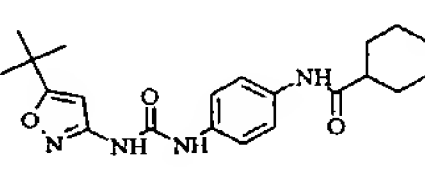
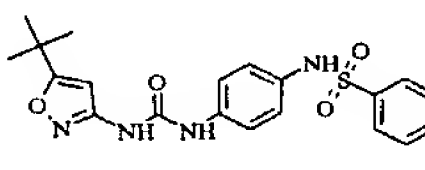
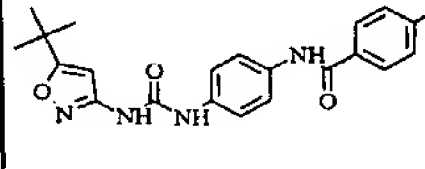
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)
	+++
	+++
	++++
	++++
	+++
	+++

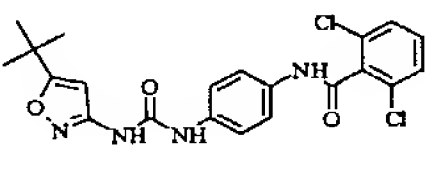
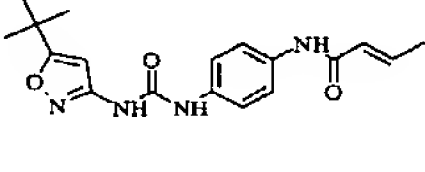
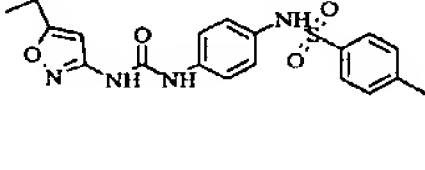
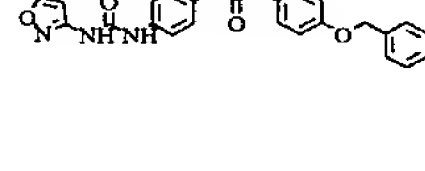
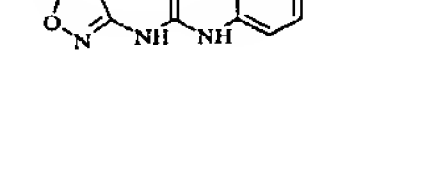

Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	+++	+
	++++	++++	+++	+
	+++	ND	ND	ND
	+++	ND	ND	ND
	++	ND	ND	ND
	+++	ND	ND	ND

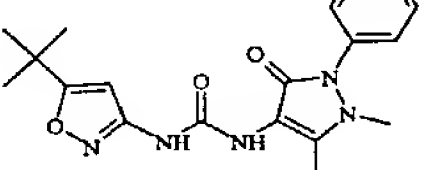
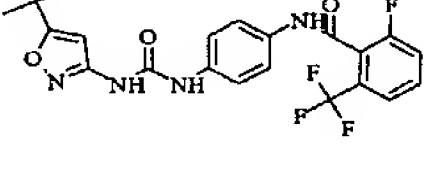
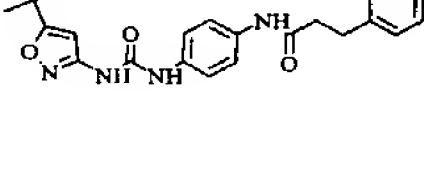
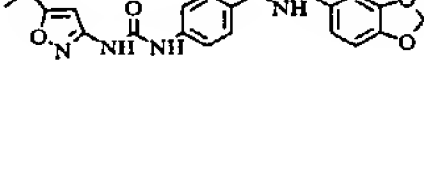
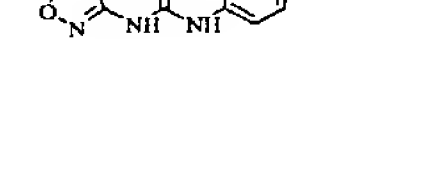
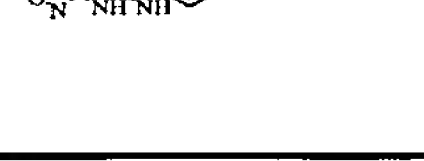
Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)	Cell Assay:CS 0001:IC ₅₀ (nM)	Cell Assay:CS 0005:IC ₅₀ (nM)	Cell Assay:CS 0002:IC ₅₀ (nM)
	++++	ND	ND	ND
	++++	++++	ND	++
	++	ND	ND	ND
	++++	++++	+++	++
	++++	++++	+++	++
	++++	++++	++++	++

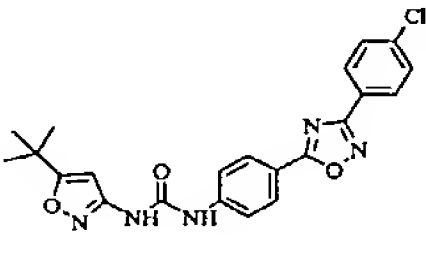
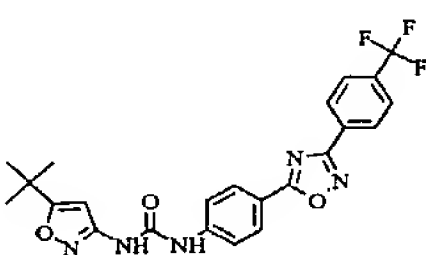
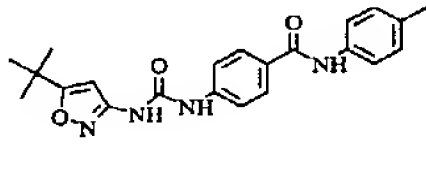
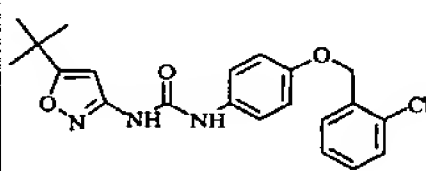
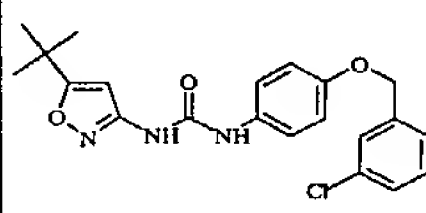
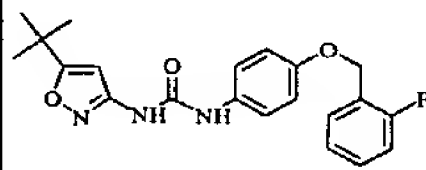
Compound Structure	Binding Assay:FLT 3(DKIN):K _d (nM)
	++
	++
	++
	+
	++
	++

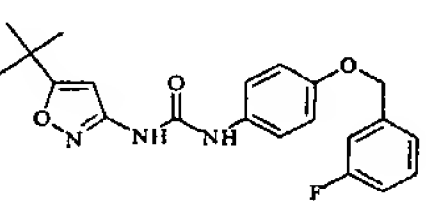
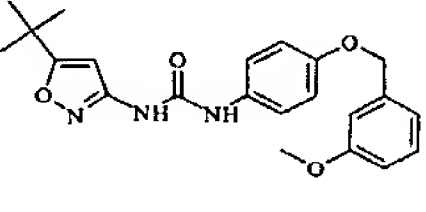
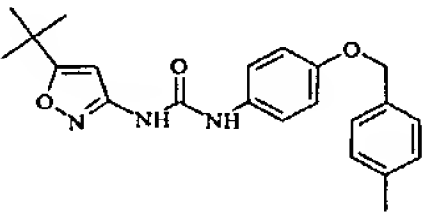
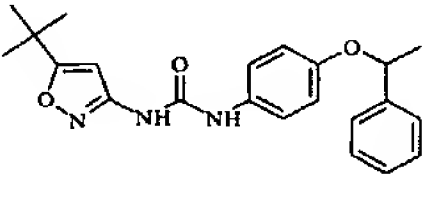
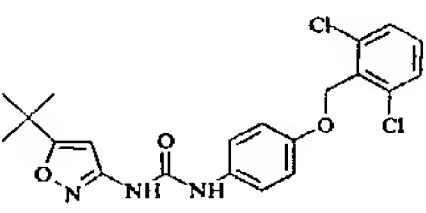
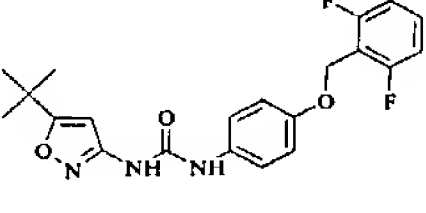
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)
	++++	+++
	++++	ND
	+++	ND
	+++	ND
	+++	ND
	++++	+++

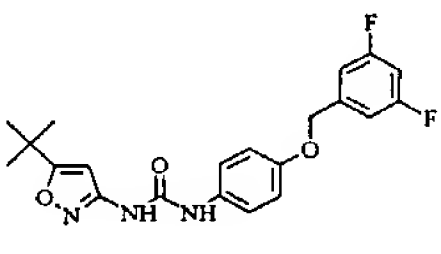
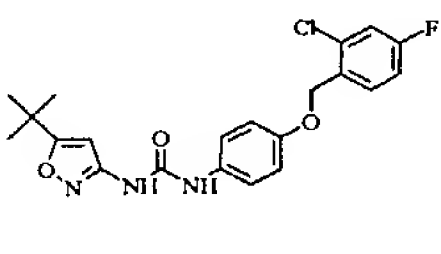
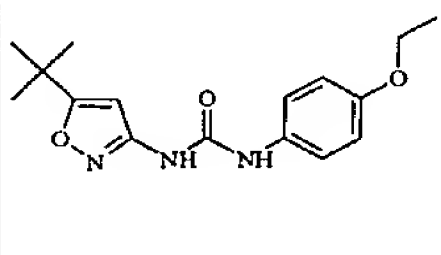
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	ND	ND	ND
	++	ND	ND	ND
	++++	++++	++++	+

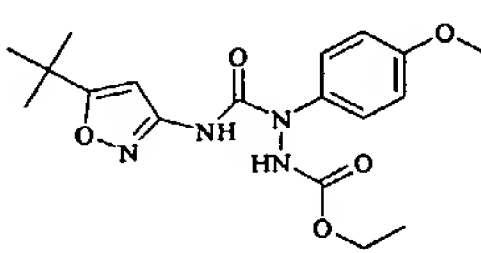
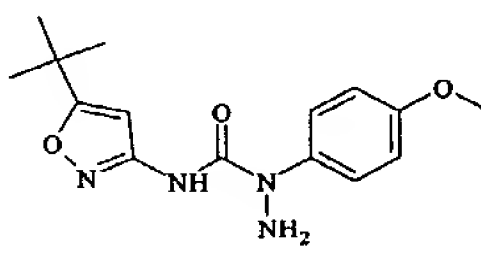
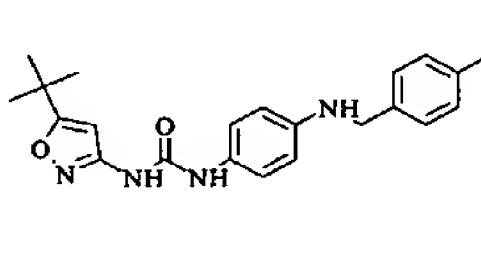
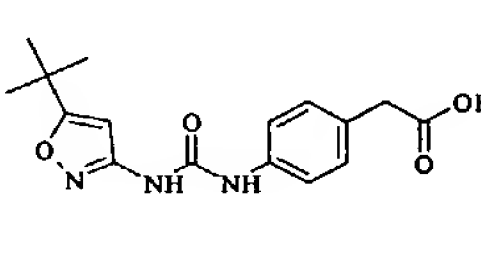
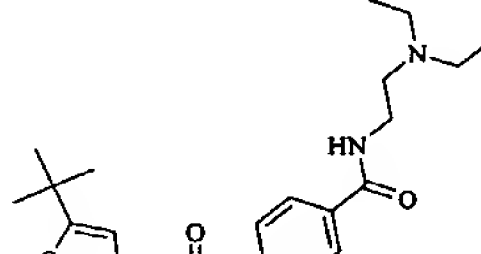
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)
	++++
	+++
	++
	++++
	+
	+

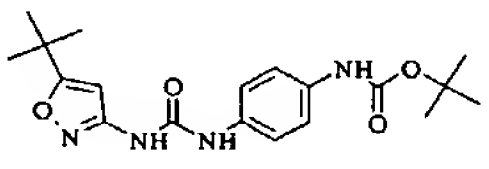
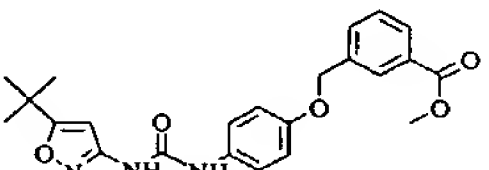


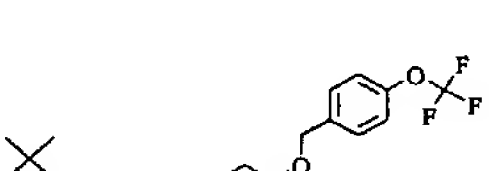
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++	ND	ND	ND
	+++	ND	ND	ND
	++++	++++	ND	ND
	+++	ND	ND	ND
	++++	++++	+++	++
	++++	++++	ND	+

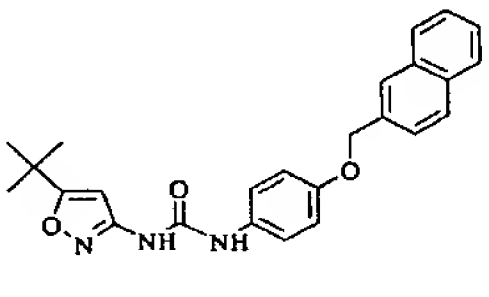
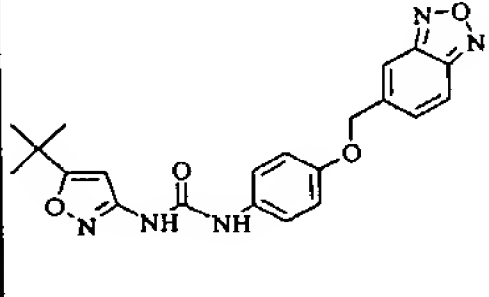
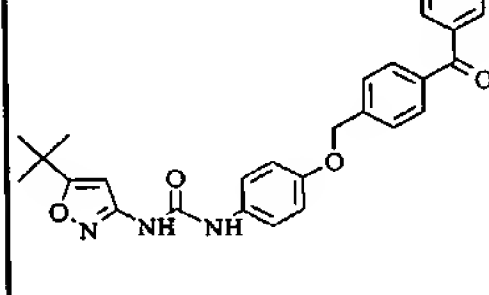
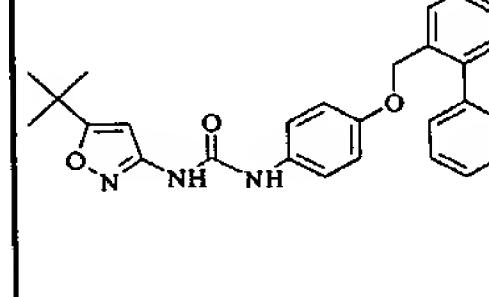
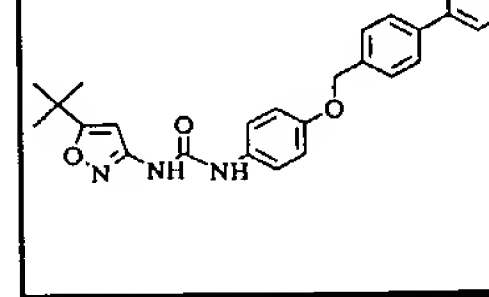
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	++++	+++	+
	+++	ND	ND	ND
	++++	++++	ND	ND
	++++	++++	+++	++
	++++	++++	+++	ND
	++++	++++	++++	++

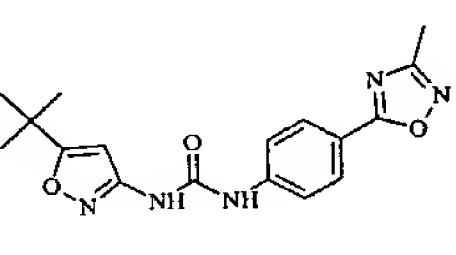
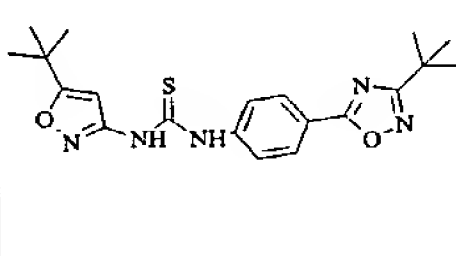
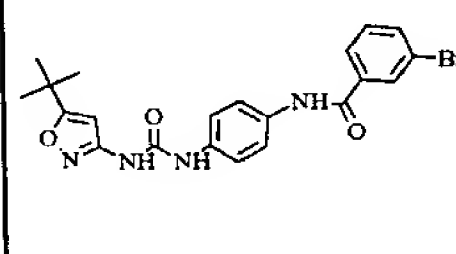
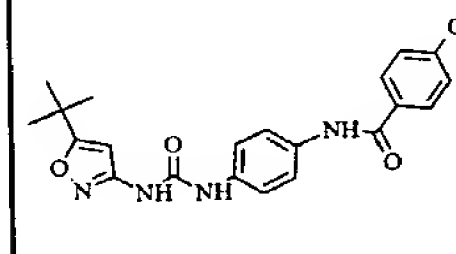
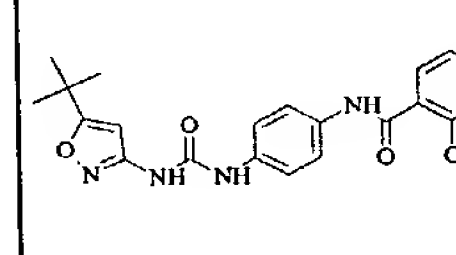
Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)
	++++	++++	+++
	++++	++++	ND
	++++	++++	ND
	++++	ND	ND
	++++	ND	ND
	++++	++++	ND

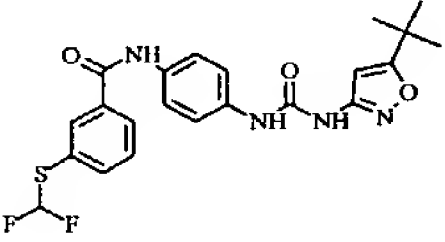
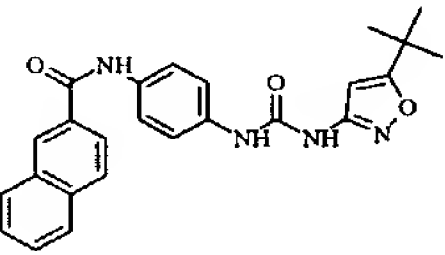
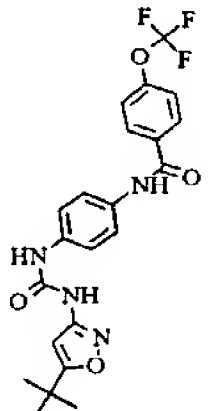
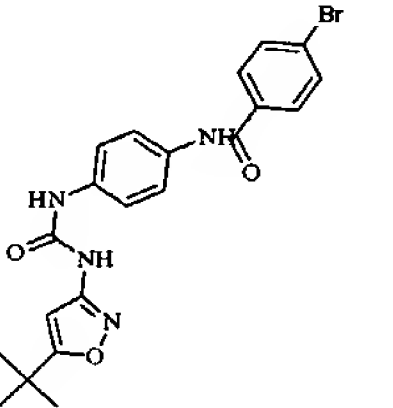
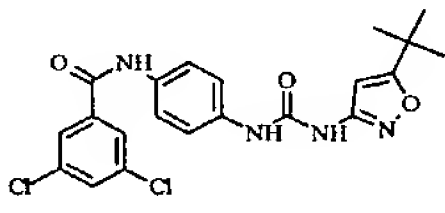
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	+++++	+++++	+++	++
	+++++	+++	ND	ND
	+++++	+++++	ND	ND

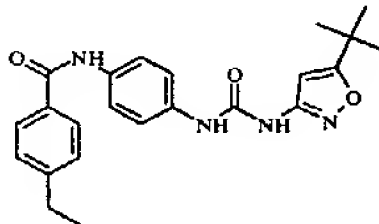
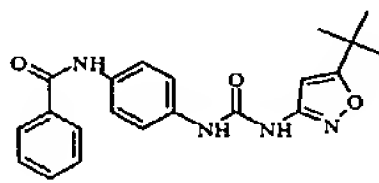
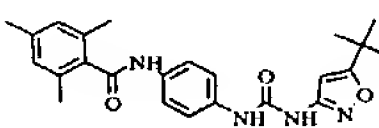
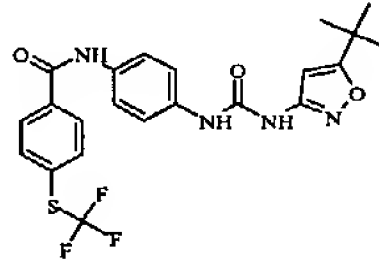
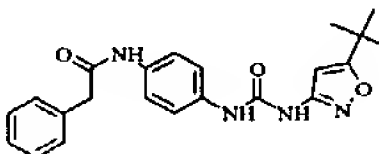
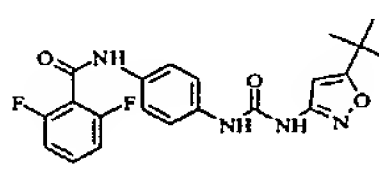
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)
	+++
	+++
	+++++
	++
	+

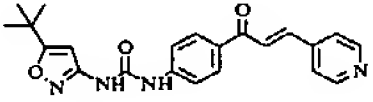
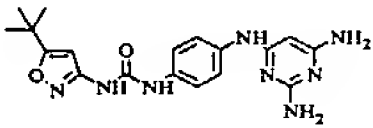
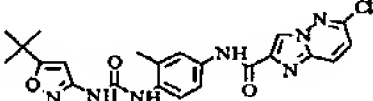
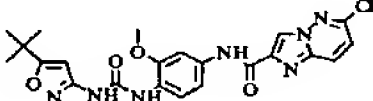
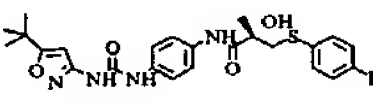
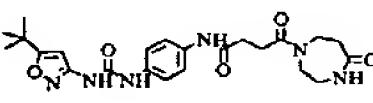
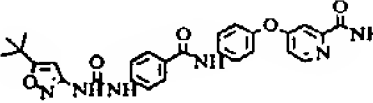
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)
	++++	+++
	++++	+++
	+++	++
	++++	+++
	++++	+++

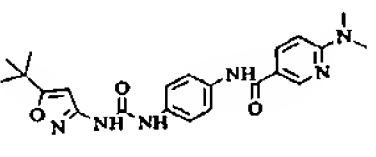
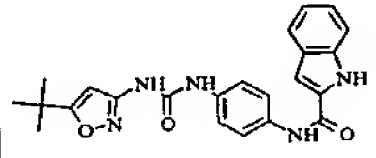
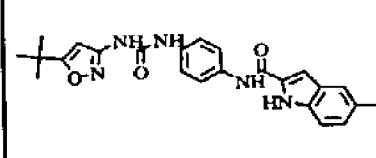
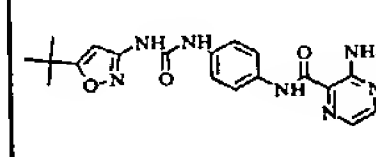
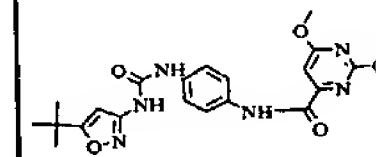
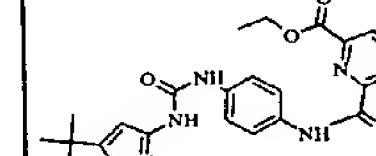
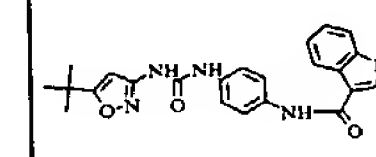
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	+++++	+++++	+++++	++
	+++++	+++	ND	ND
	+++++	+++	ND	ND
	+++	++	ND	ND
	+++++	+++++	+++++	ND

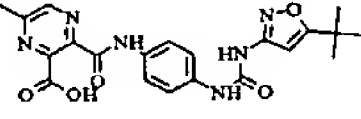
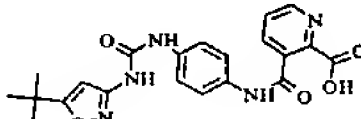
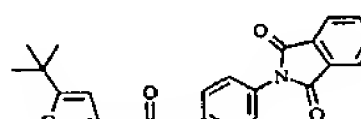
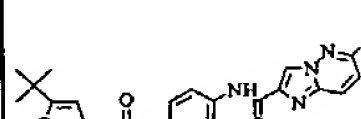



Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	+++	ND	ND
	++	+++	ND	ND
	+++	++	ND	ND
	++	++	+++	ND
	++++	++++	ND	++

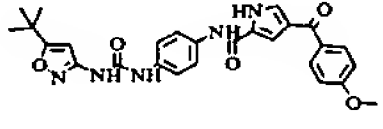
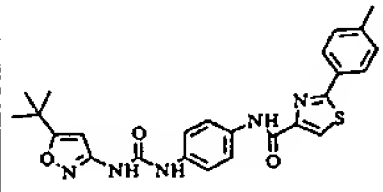
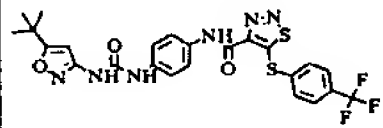
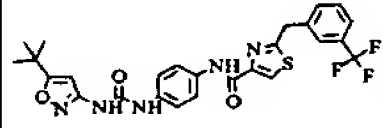
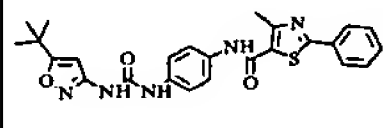
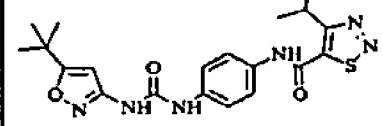
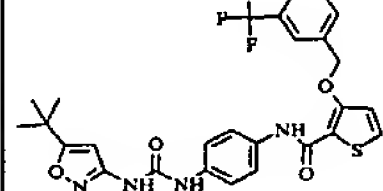
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)
	++++	+++	ND
	++++	++++	++++
	++	++	ND
	++	++	ND
	+++	+++	ND

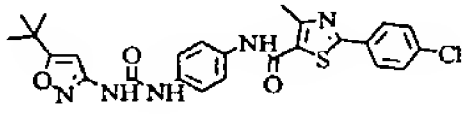
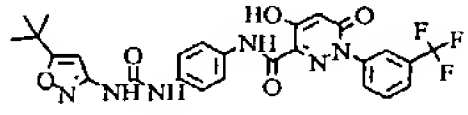
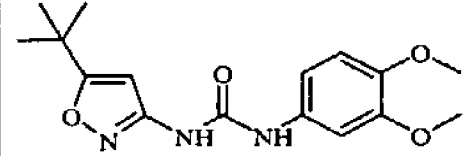
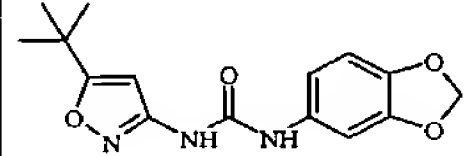
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)
	++++	+++	ND	+
	++++	++++	++++	ND
	+++	++	ND	ND
	+++	+	ND	ND
	+++	++	ND	ND
	+++	++	ND	ND

Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminus):Kd (nM)
	ND	+++	ND	+	++++
	ND	++++	ND	+	++++
	ND	+++	ND	ND	+++
	ND	+++	ND	ND	++
	ND	+++	ND	ND	++++
	ND	++	ND	ND	+++
	ND	+++	ND	++	++++

Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminu s):Kd (nM)
	ND	++++	++++	++	++++
	ND	++++	++++	++	++++
	ND	++++	++++	++	++++
	ND	++++	++++	+	++++
	ND	++++	++++	++	++++
	ND	++++	ND	++	++++
	ND	++++	++++	++	++++

Compound Structure	Binding Assay:FLT 3(DKIN):Kd (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminus):Kd (nM)
	ND	++++	++++	+	++++
	ND	++++	ND	+	+++
	ND	++++	ND	+	++++
	ND	++	ND	ND	ND
	ND	+++	ND	ND	+++
	ND	++	ND	ND	+++
	ND	+	ND	ND	+++

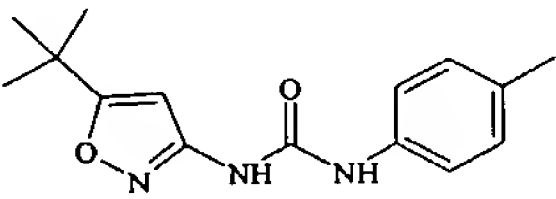
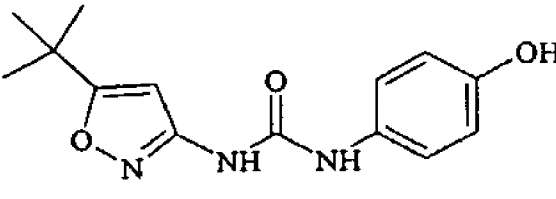
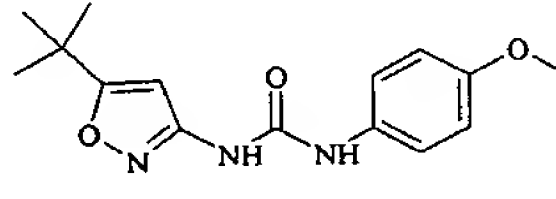
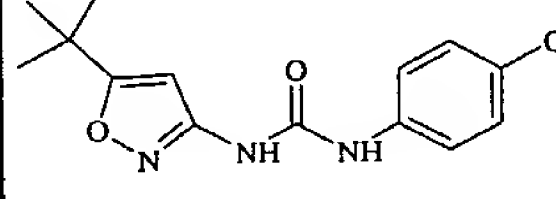
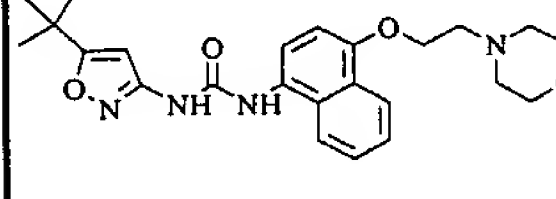
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminu s):Kd (nM)
	ND	++	ND	ND	+++
	ND	+++	ND	++	++++
	ND	+++	ND	ND	+++
	ND	+++	ND	ND	++++
	ND	++++	ND	++	++++
	ND	++	ND	ND	+++
	ND	++	ND	ND	++++

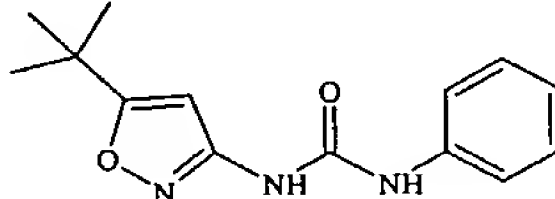
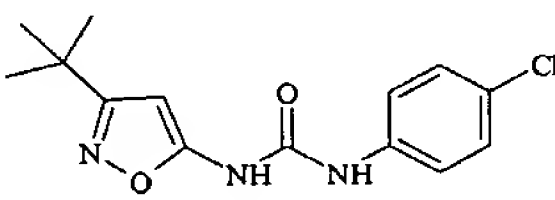
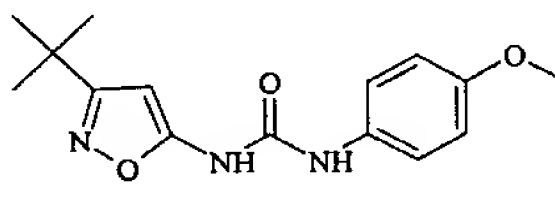
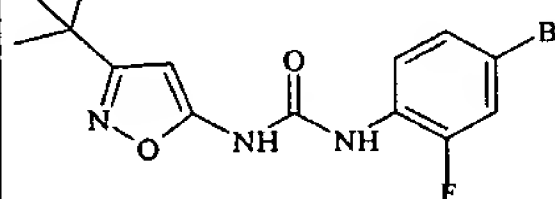
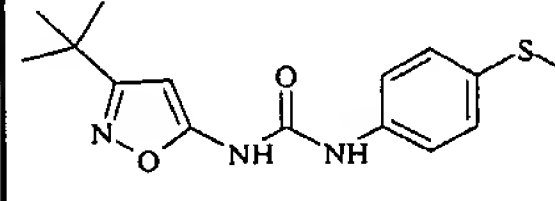
Compound Structure	Binding Assay:FLT 3(DKIN):K d (nM)	Cell Assay:CS 0001:IC50 (nM)	Cell Assay:CS 0005:IC50 (nM)	Cell Assay:CS 0002:IC50 (nM)	Binding Assay:FLT 3(JMminu s):Kd (nM)
	ND	++++	ND	++	++++
	ND	++	ND	ND	+++
	ND	+	ND	ND	++
	ND	+++	ND	+	+++

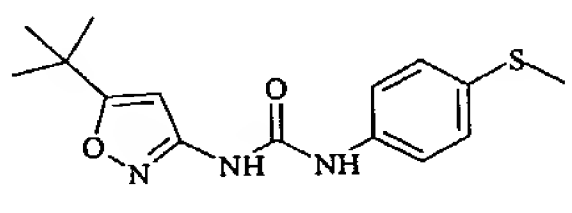
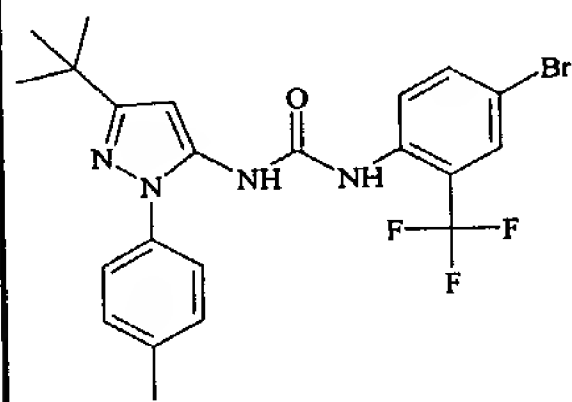
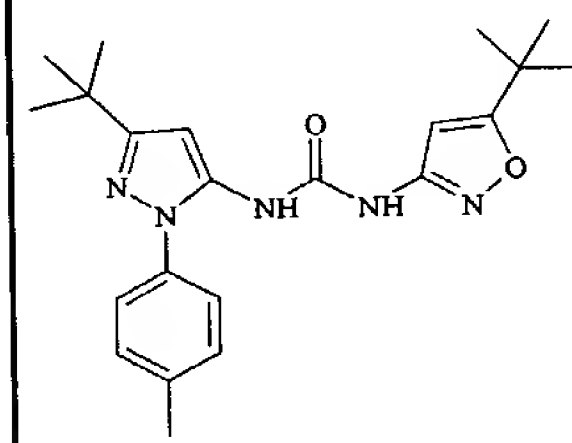
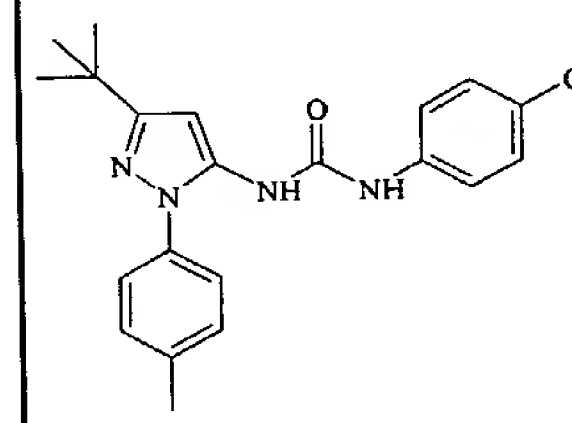
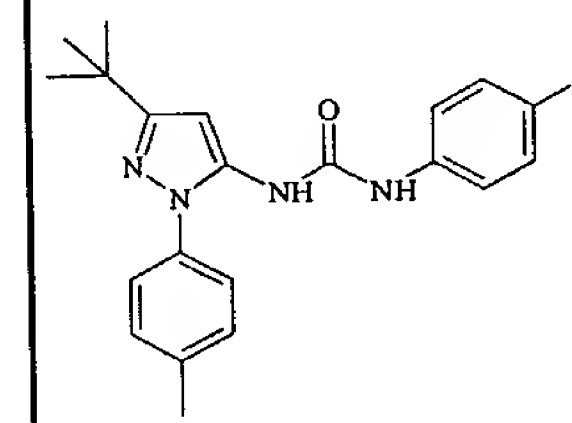
The Affinity of the Compounds for PDGFR

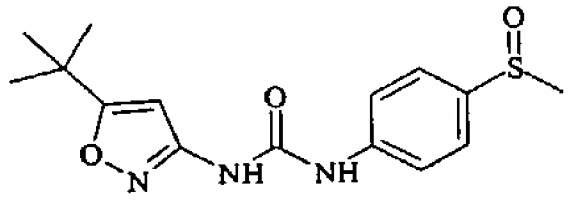
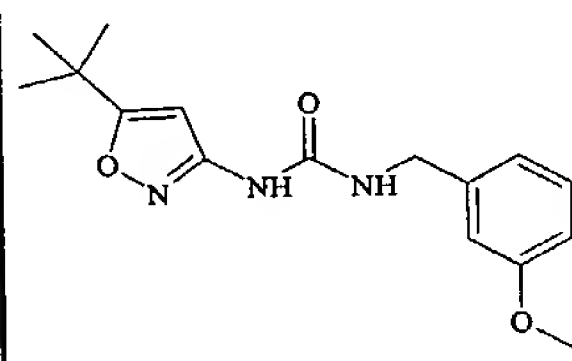
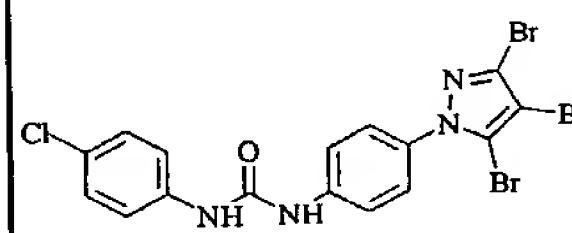
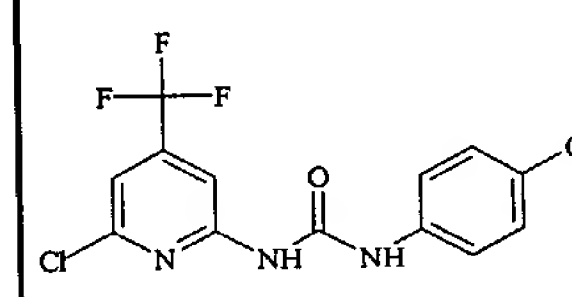
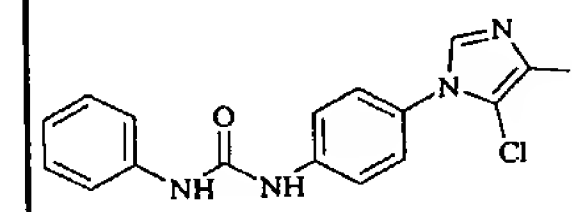
K_d values for the interactions between PDGFR- β and candidate small molecule ligands were measured by a phage-display-based competitive binding assay that is described in detail in U.S. Serial No. 10/406,797 filed 2 April 2003 and incorporated herein by reference.

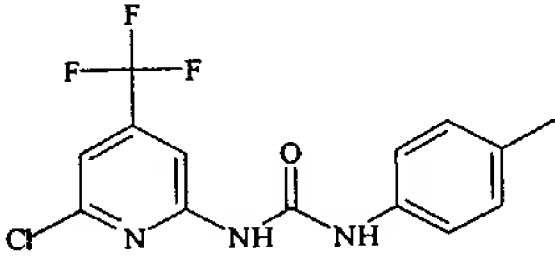
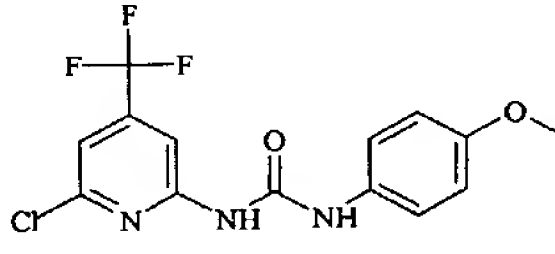
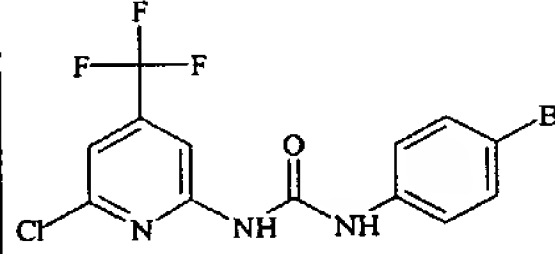
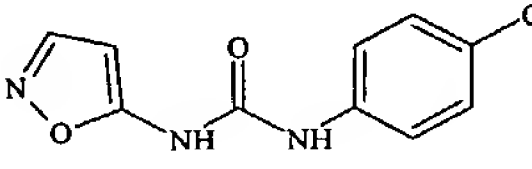
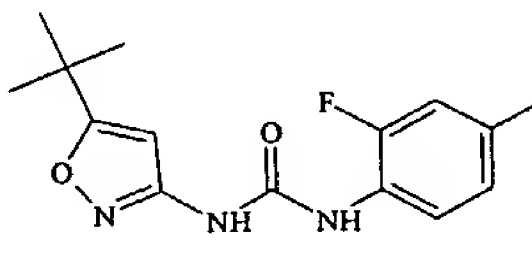
5 Briefly, T7 phage displaying human PDGFR- β were incubated with an affinity matrix coated with known PDGFR- β inhibitor in the presence of various concentrations of the soluble competitor molecules. Soluble competitor molecules that bind PDGFR- β prevent binding of PDGFR- β phage to the affinity matrix, hence, after washing, fewer phage are recovered in the phage eluate in the presence of an effective competitor than in the absence of an effective competitor. The K_d for the interaction between the soluble competitor molecule and
10 PDGFR- β is equal to the concentration of soluble competitor molecule that causes a 50% reduction in the number of phage recovered in the eluate compared to a control sample lacking soluble competitor. K_d values for the interaction between PDGFR- β and several small molecules are shown below.

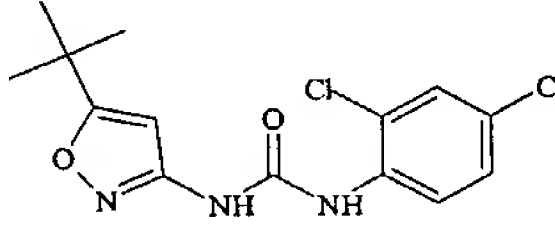
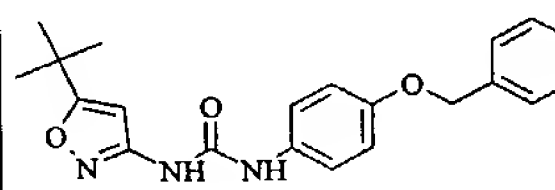
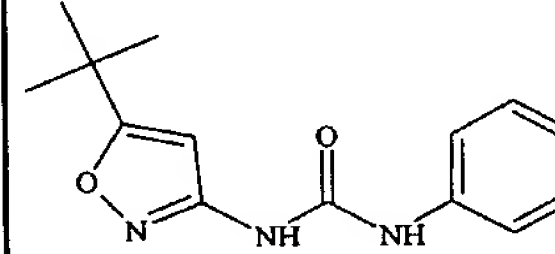
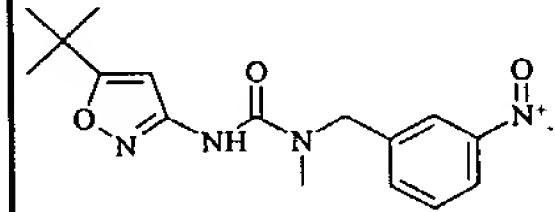
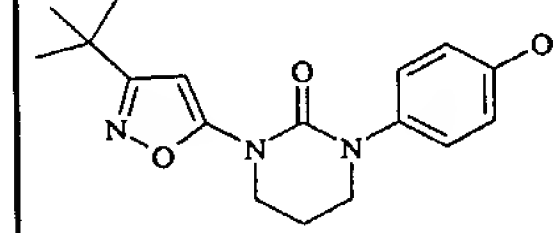
Compound Structure	Binding Assay:PDGFRB (DKIN)
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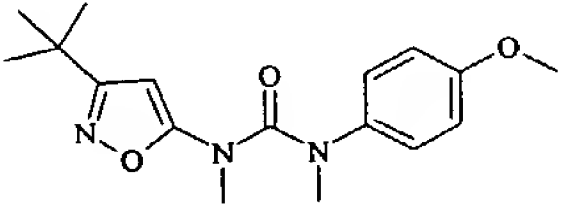
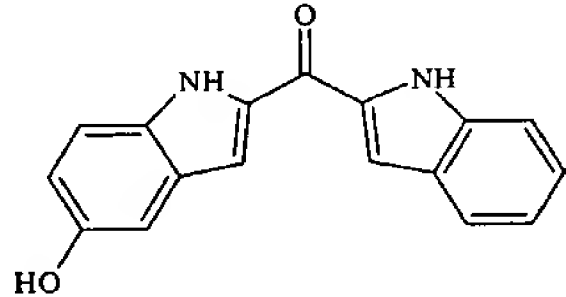
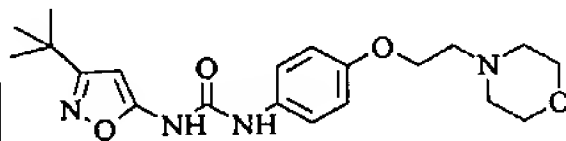
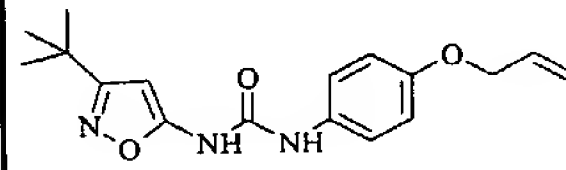
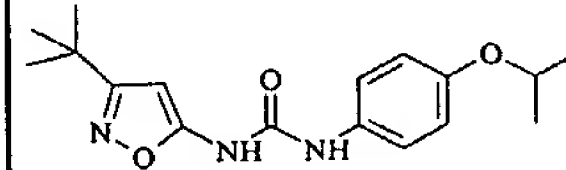
Compound Structure	Binding Assay:PDGFRB (DKIN)
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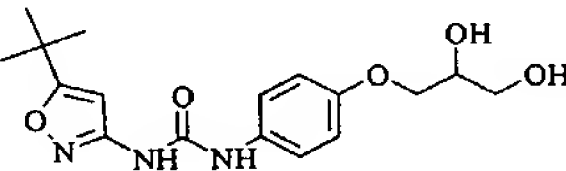
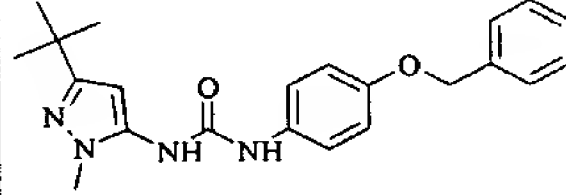
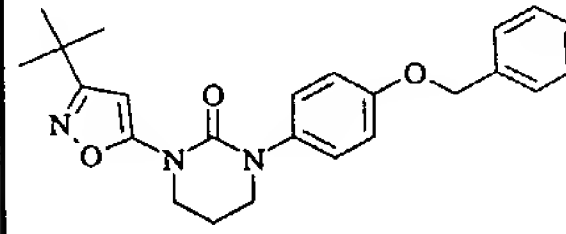
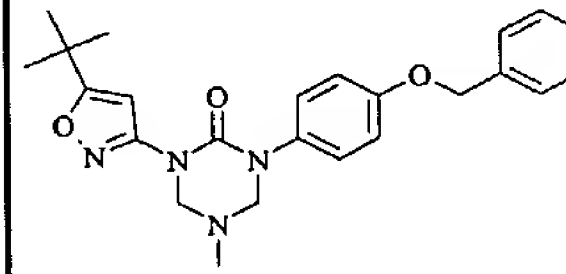
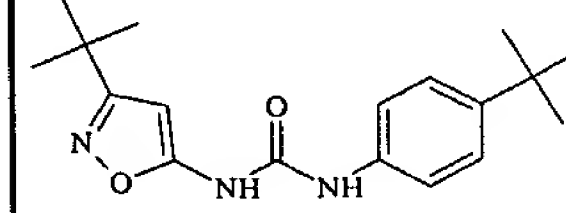
Compound Structure	Binding Assay:PDGFRB (DKIN)
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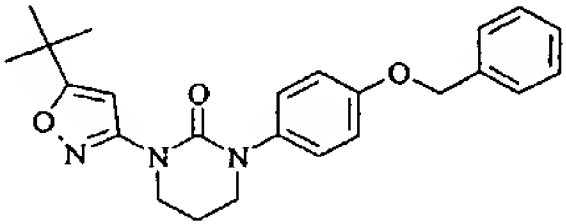
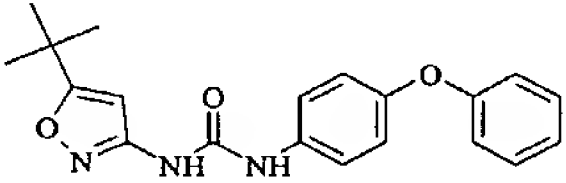
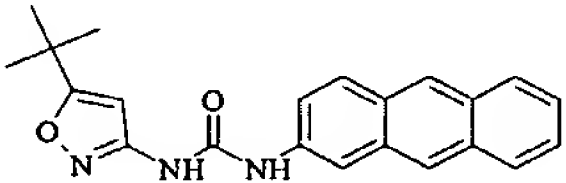
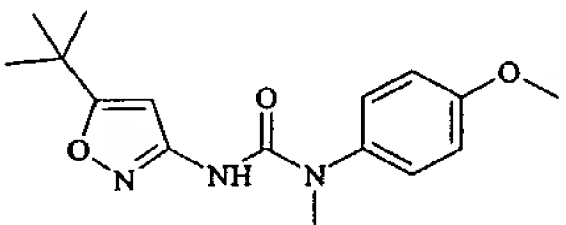
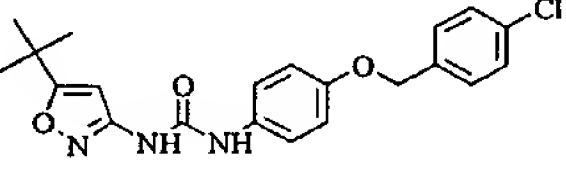
Compound Structure	Binding Assay:PDGFRB (DKIN)
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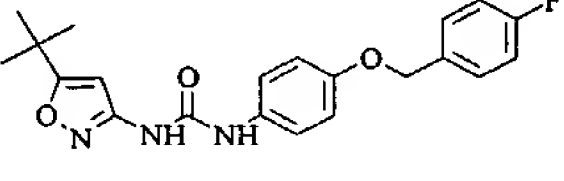
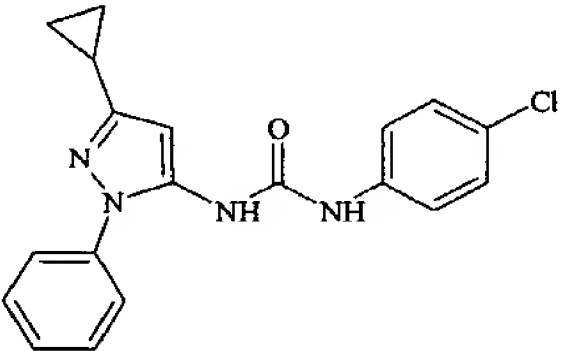
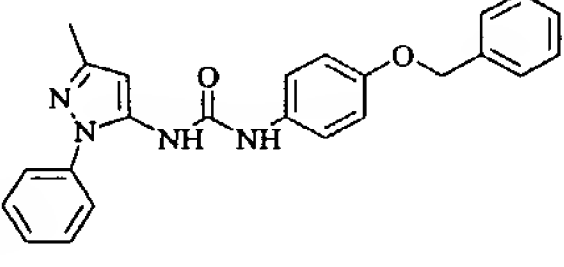
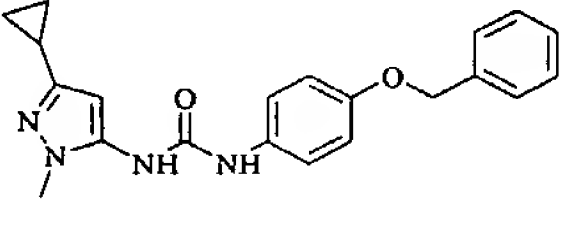
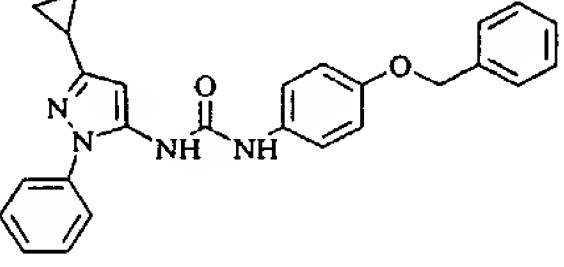
Compound Structure	Binding Assay:PDGFRB (DKIN)
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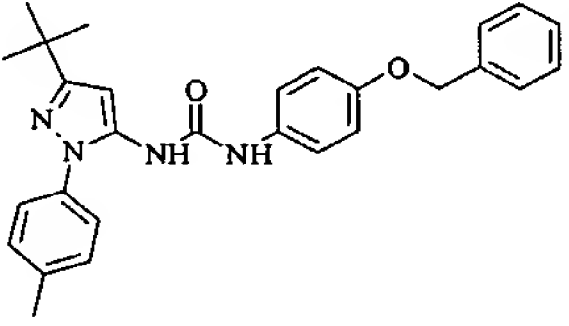
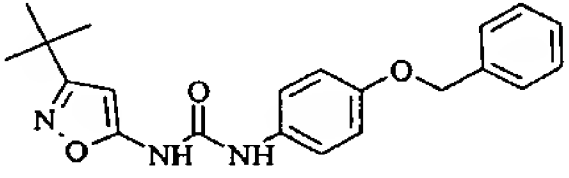
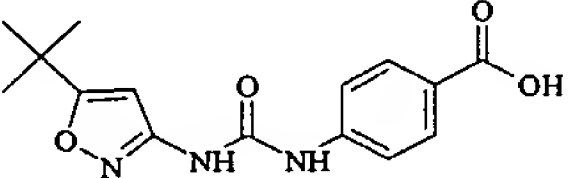
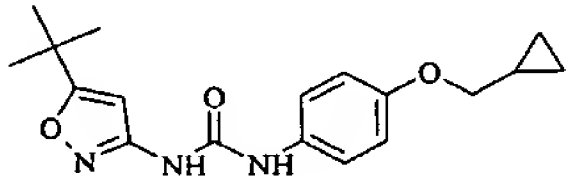
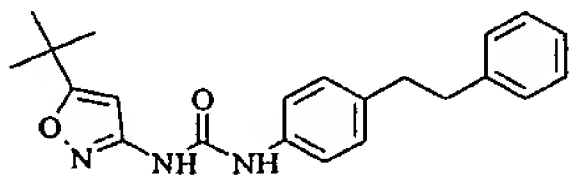
Compound Structure	Binding Assay:PDGFRB (DKIN)
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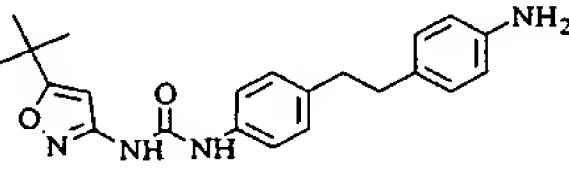
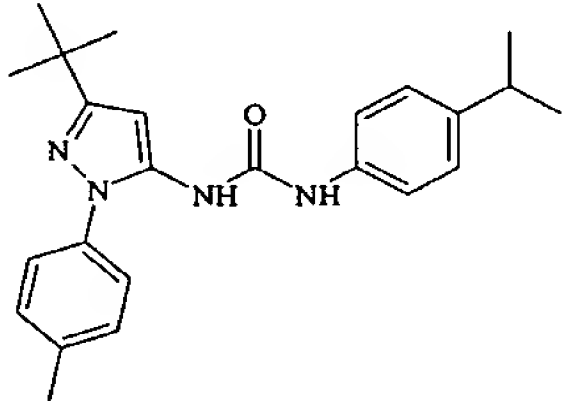
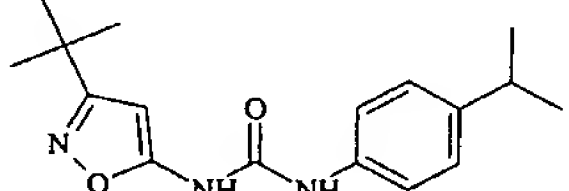
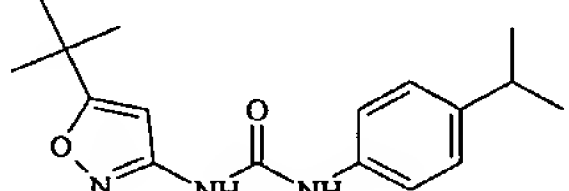
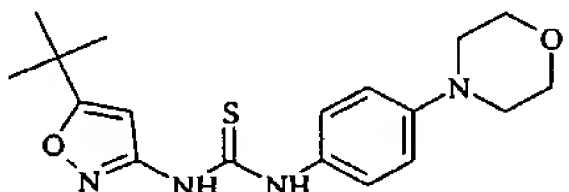
Compound Structure	Binding Assay:PDGFRB (DKIN)
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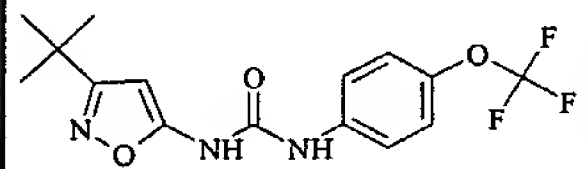
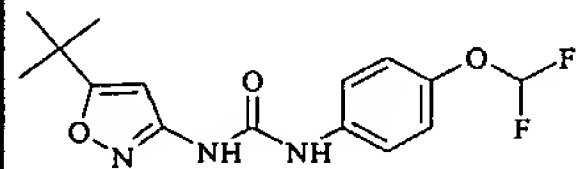
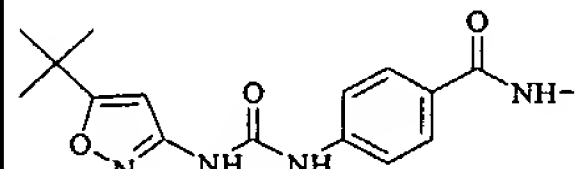
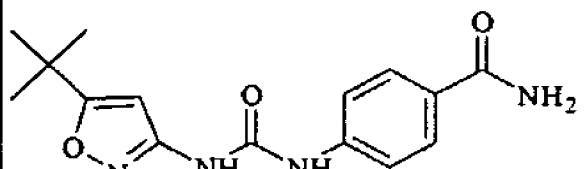
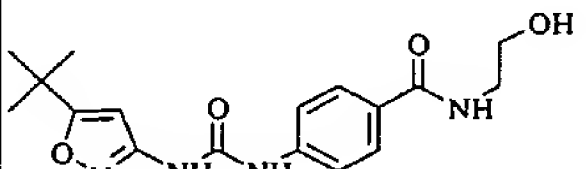
Compound Structure	Binding Assay:PDGFRB (DKIN)
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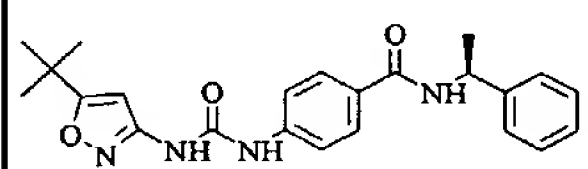
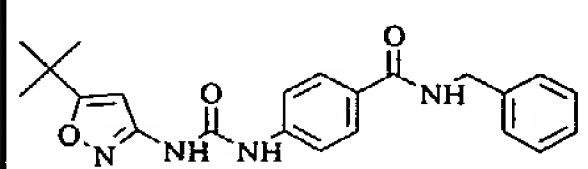
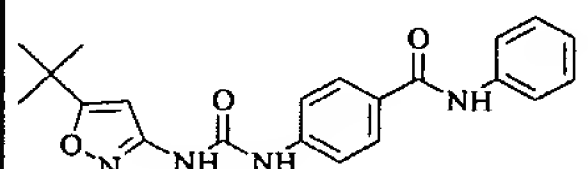
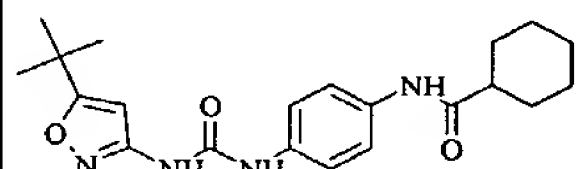
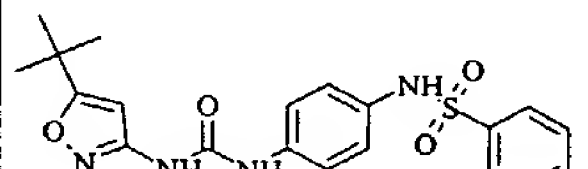
Compound Structure	Binding Assay:PDGFRB (DKIN)
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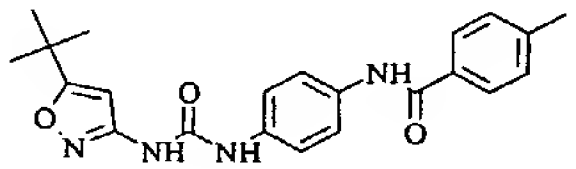
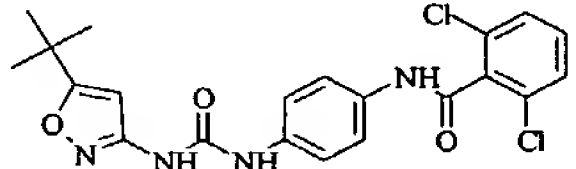
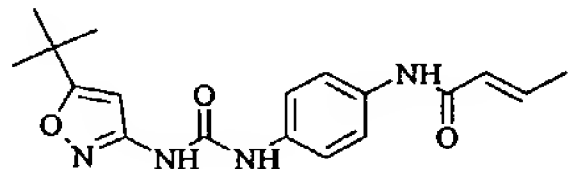
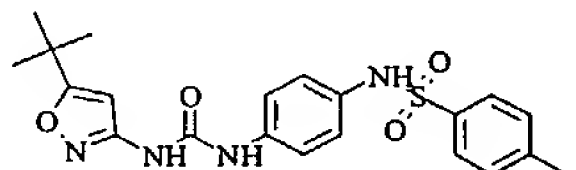
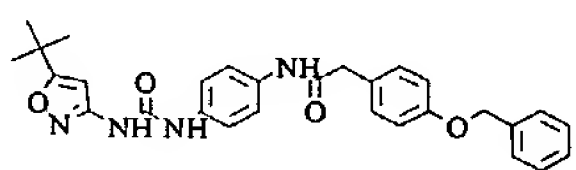
Compound Structure	Binding Assay:PDGFRB (DKIN)
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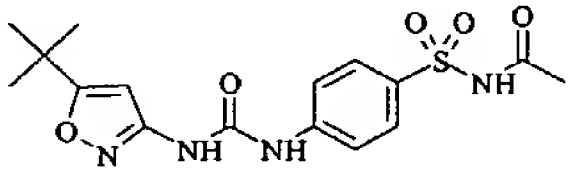
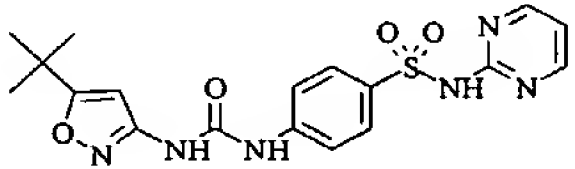
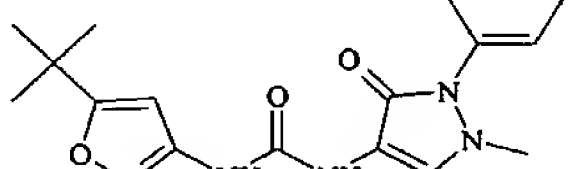
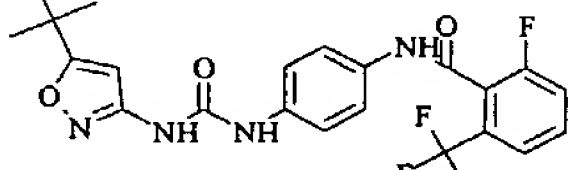
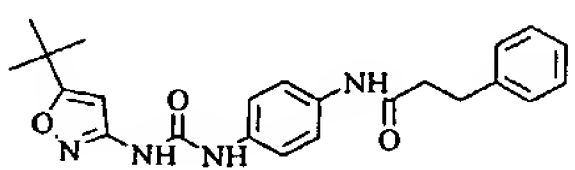
Compound Structure	Binding Assay:PDGFRB (DKIN)
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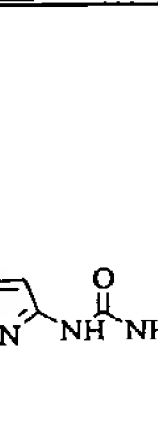
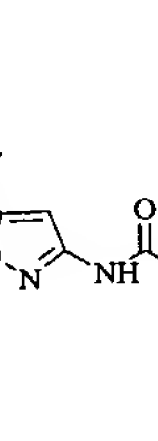
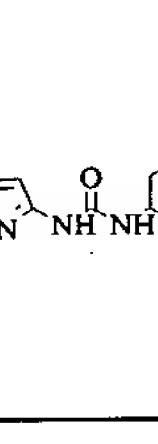
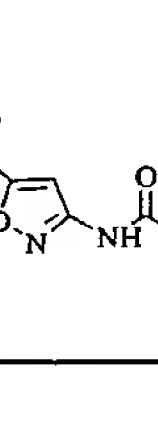
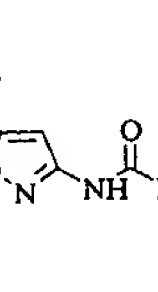
Compound Structure	Binding Assay:PDGFRB (DKIN)
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Compound Structure	Binding Assay:PDGFRB (DKIN)
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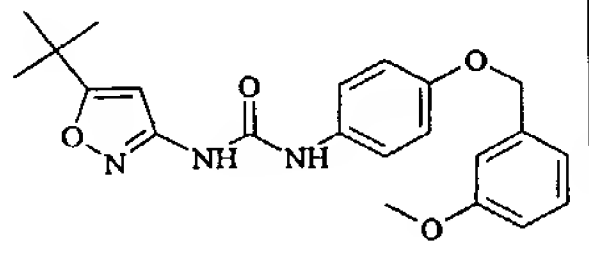
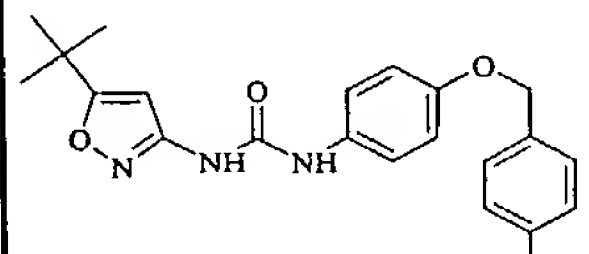
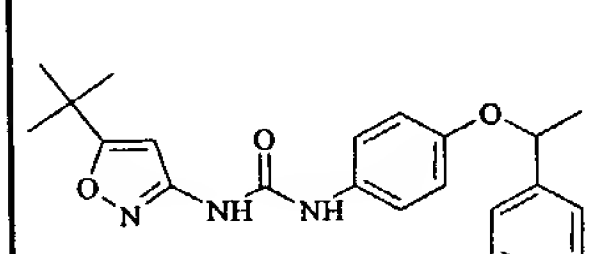
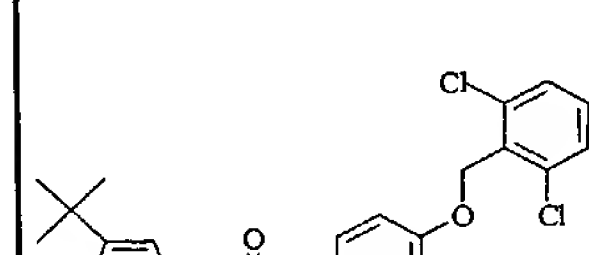
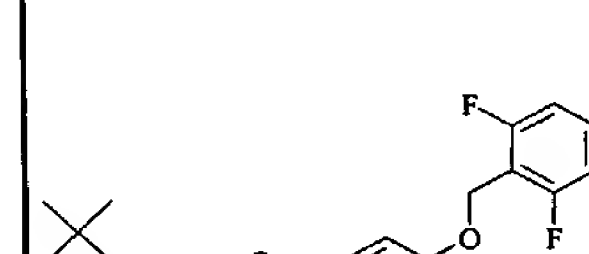
Compound Structure	Binding Assay:PDGFRB (DKIN)
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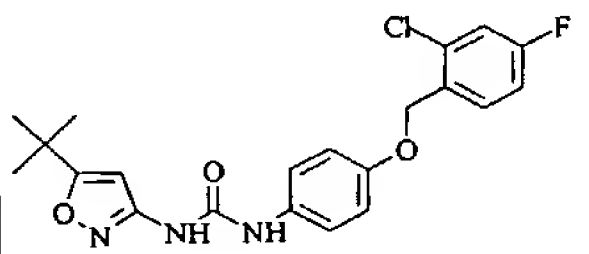
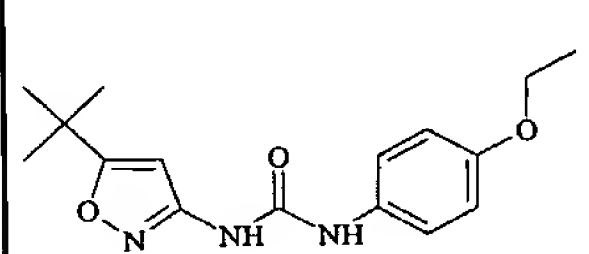
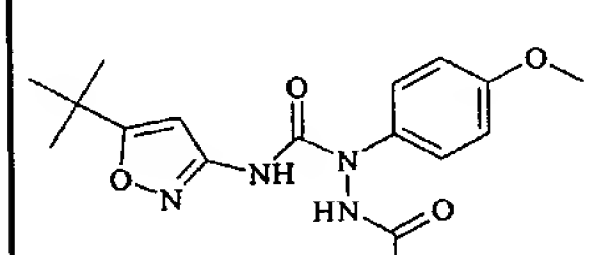
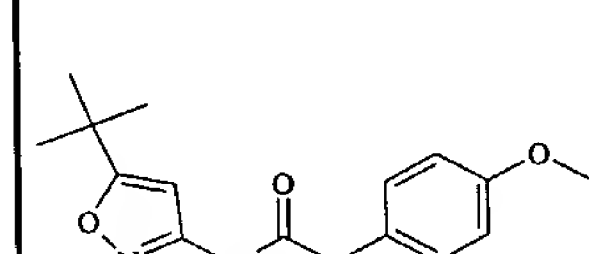
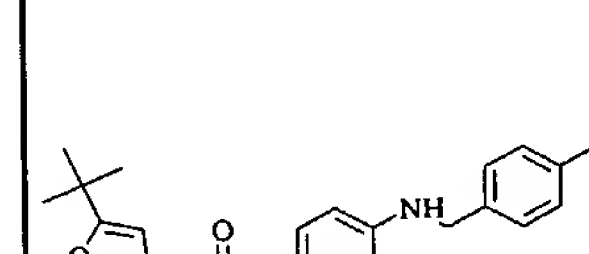
Compound Structure	Binding Assay:PDGFRB (DKIN)
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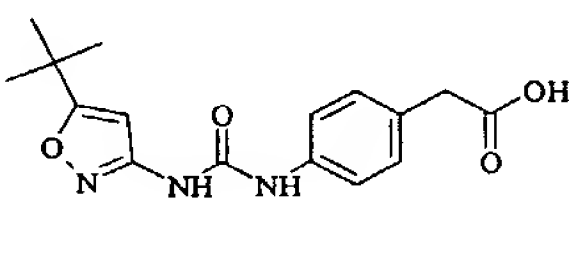
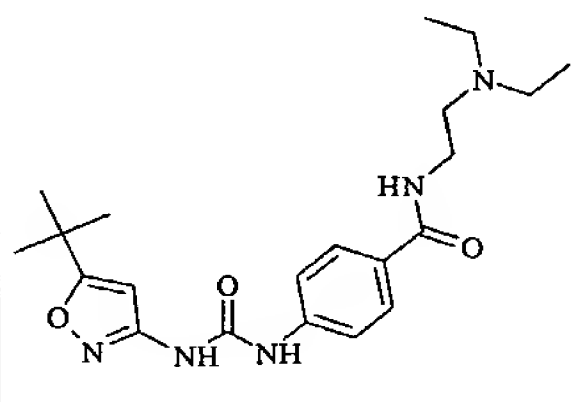
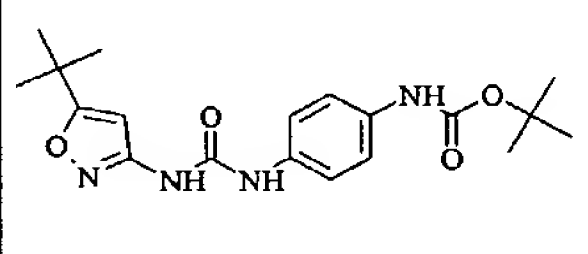
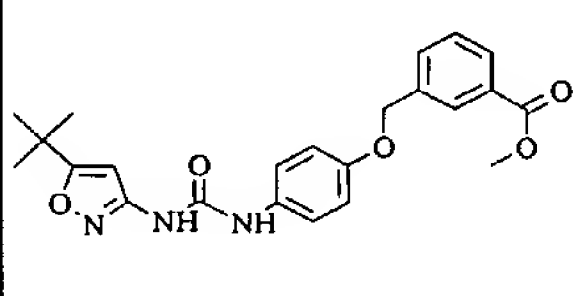
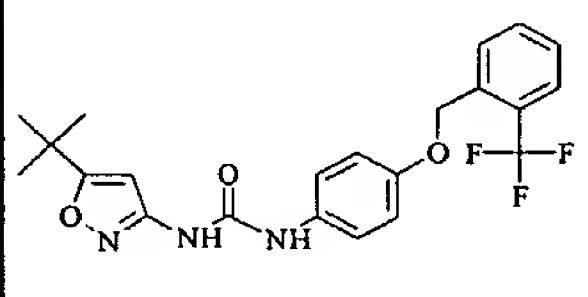
Compound Structure	Binding Assay:PDGFRB (DKIN)
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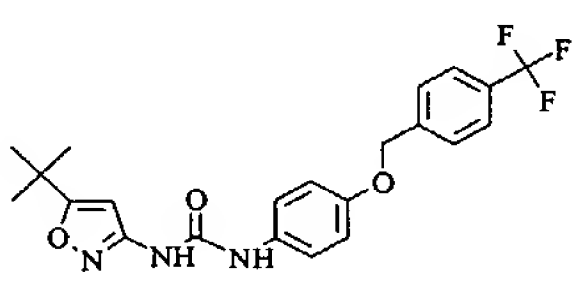
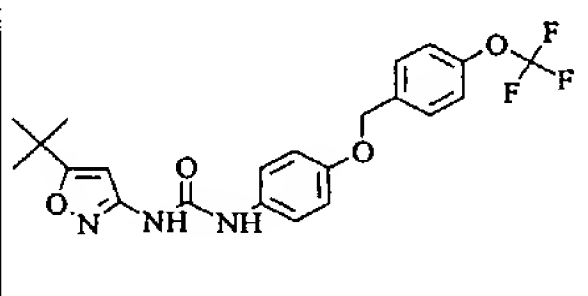
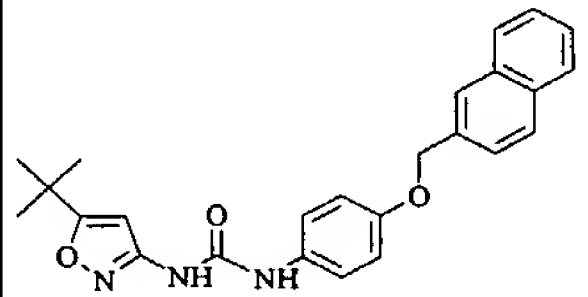
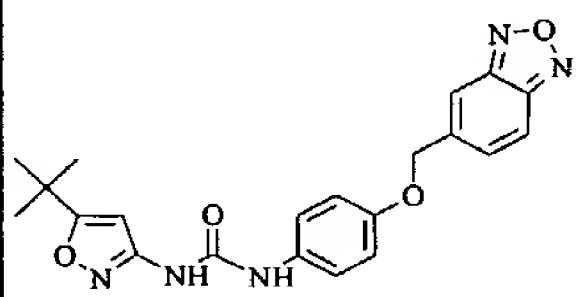
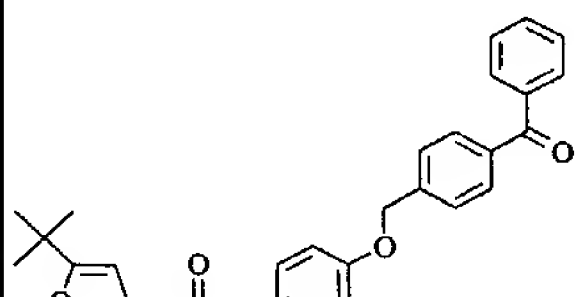
Compound Structure	Binding Assay:PDGFRB (DKIN)
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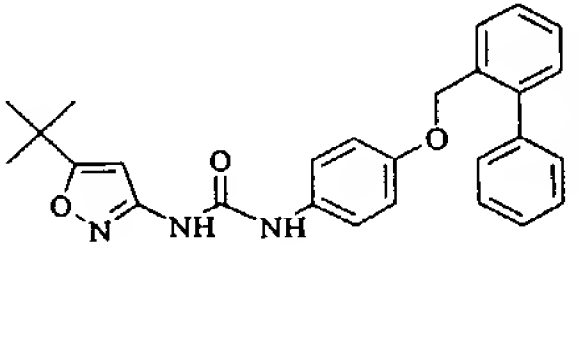
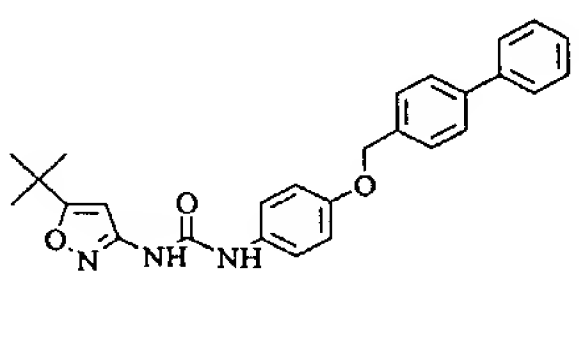
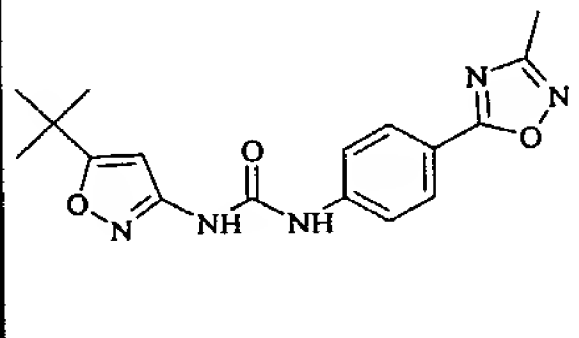
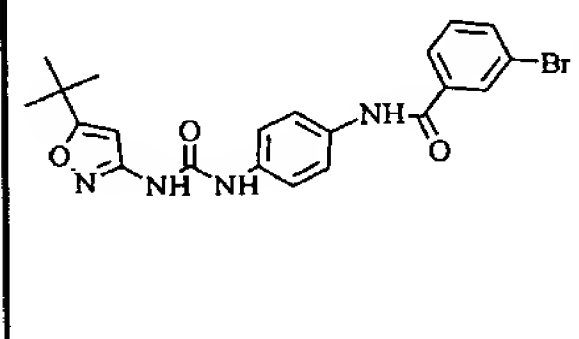
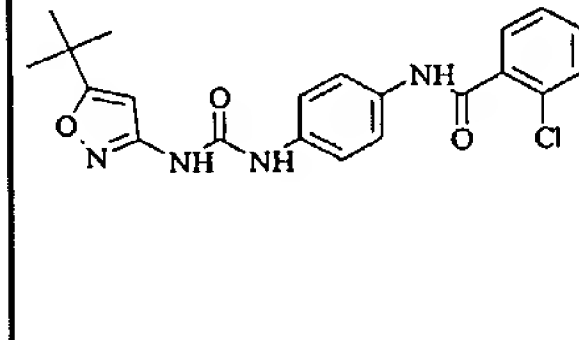
Compound Structure	Binding Assay:PDGFRB (DKIN)
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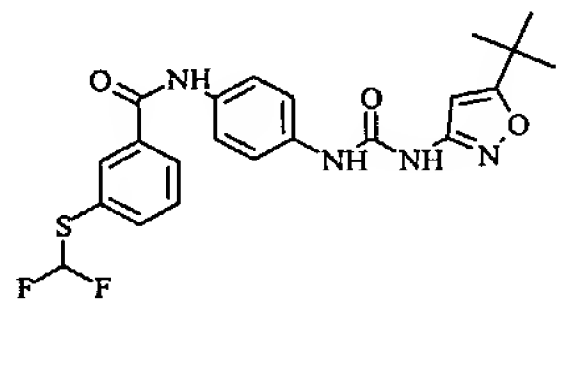
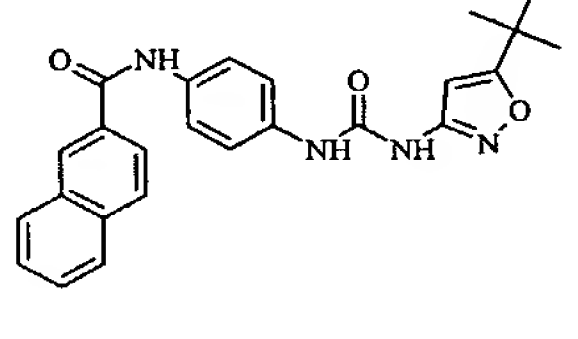
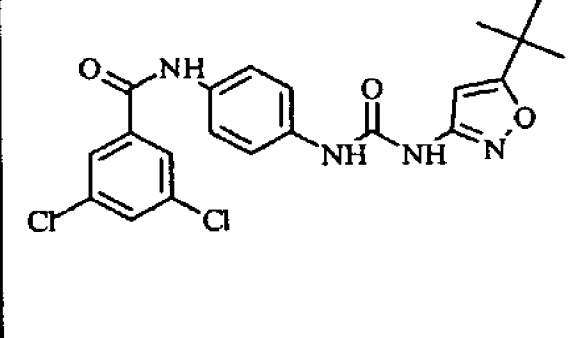
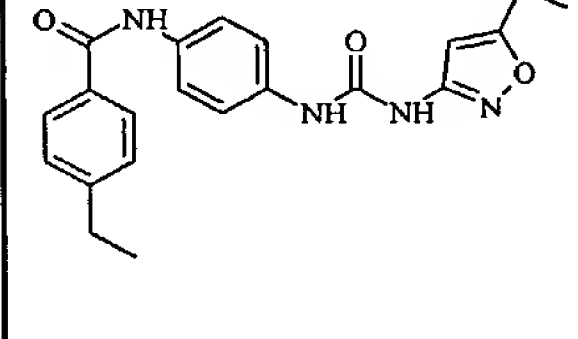
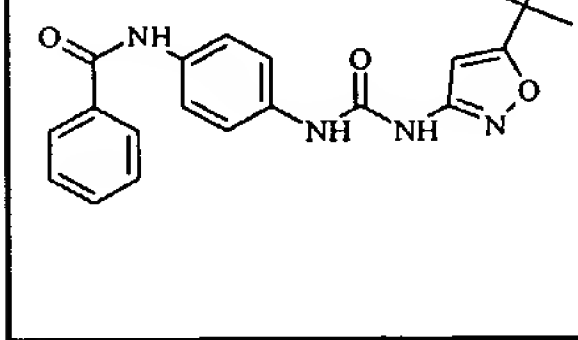
Compound Structure	Binding Assay:PDGFRB (DKIN)
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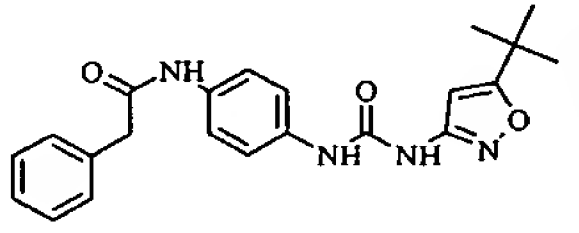
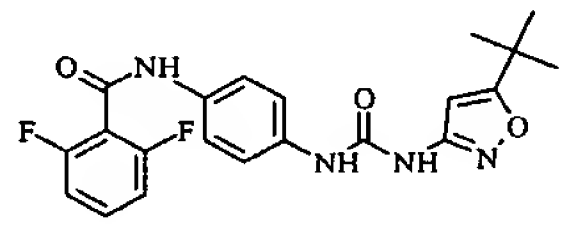
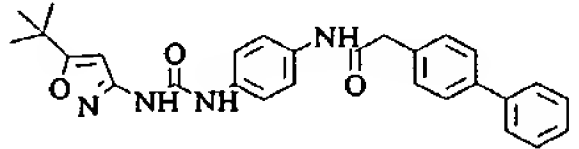
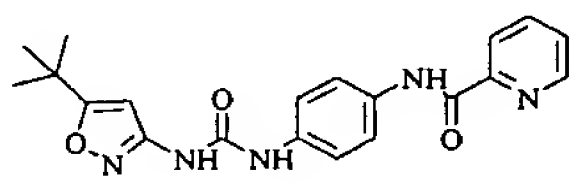
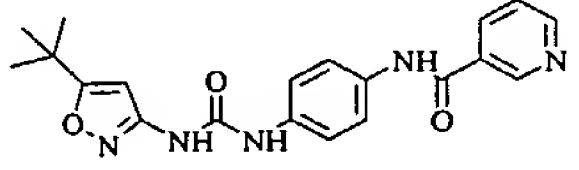
Compound Structure	Binding Assay:PDGFRB (DKIN)
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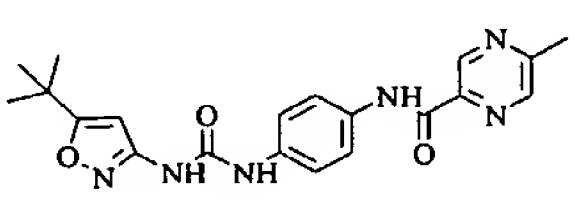
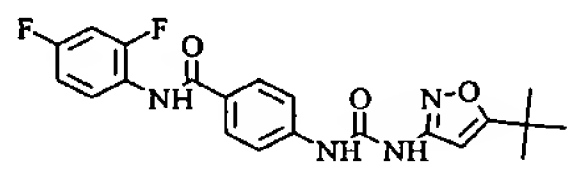
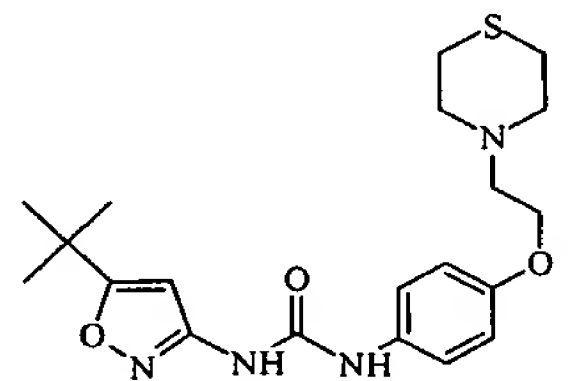
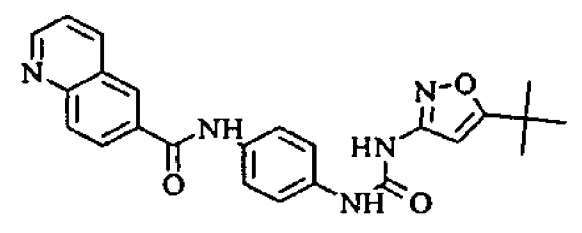
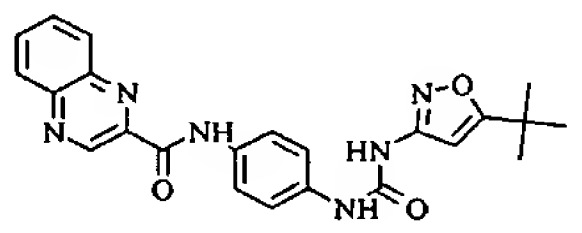
Compound Structure	Binding Assay:PDGFRB (DKIN)
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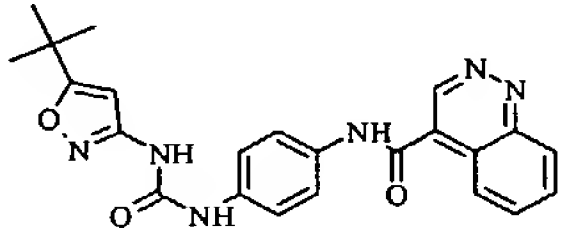
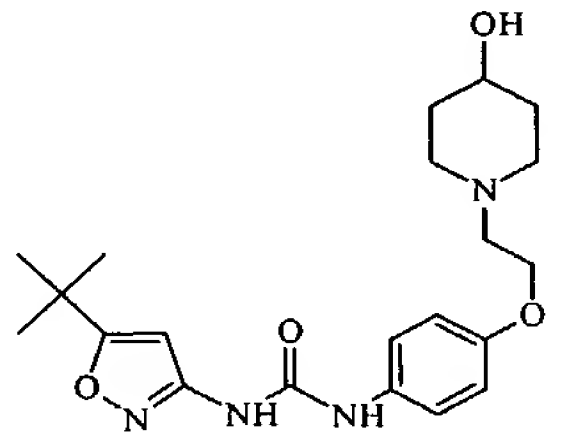
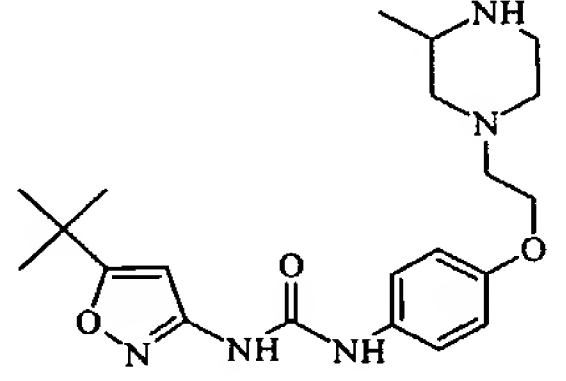
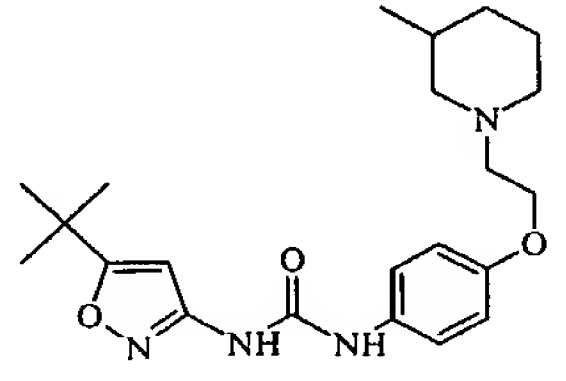
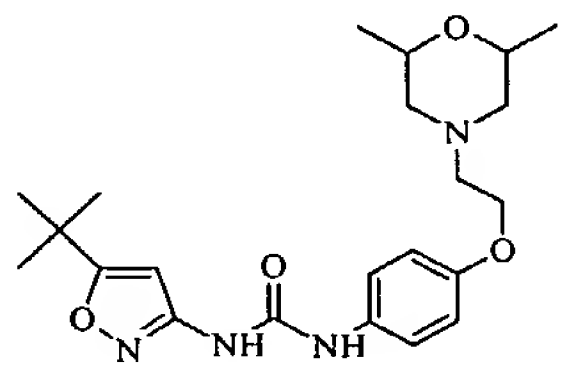
Compound Structure	Binding Assay:PDGFRB (DKIN)
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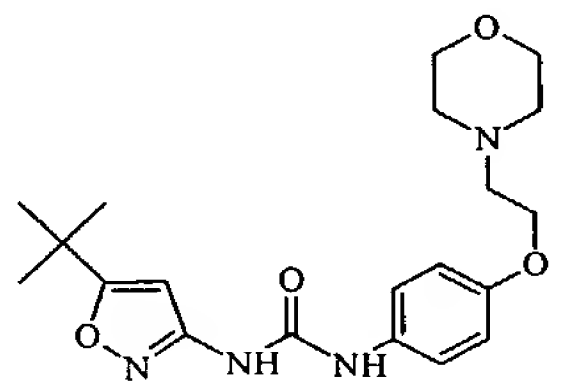
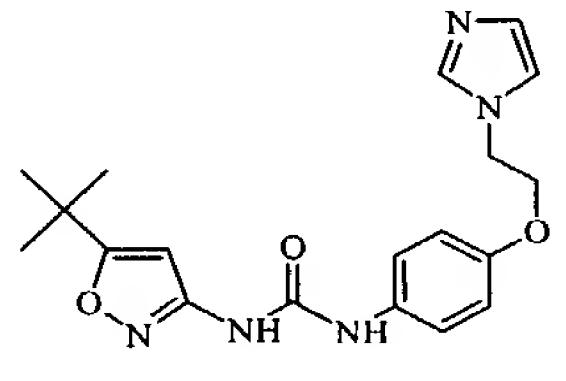
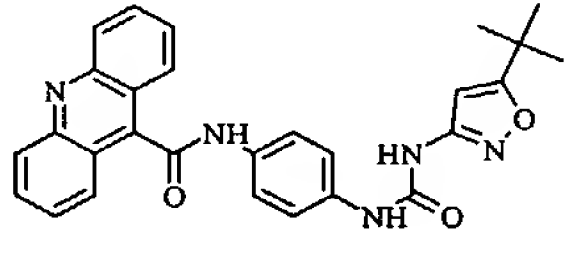
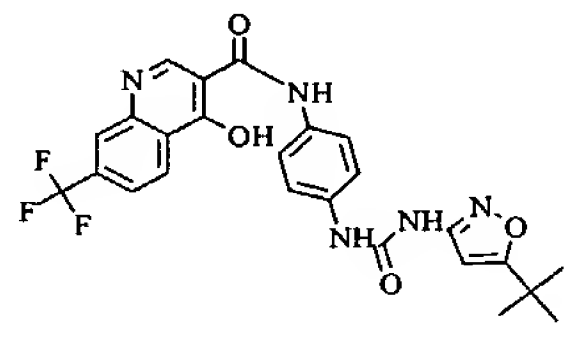
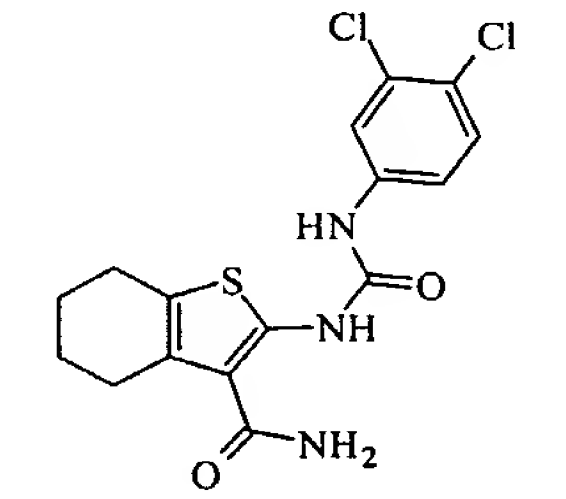
Compound Structure	Binding Assay:PDGFRB (DKIN)
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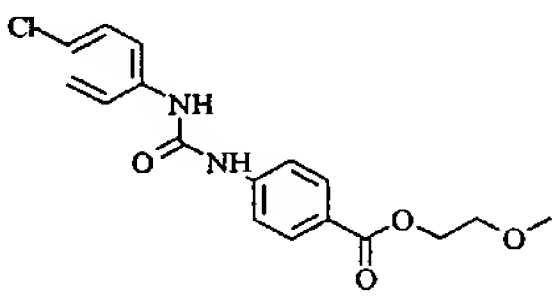
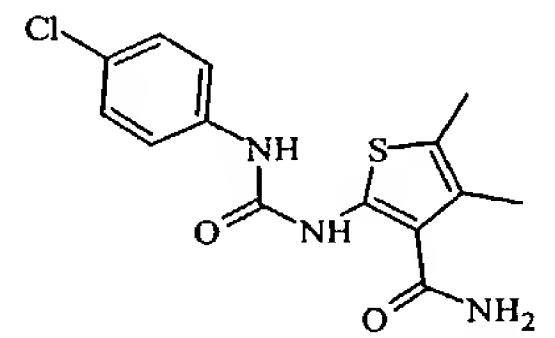
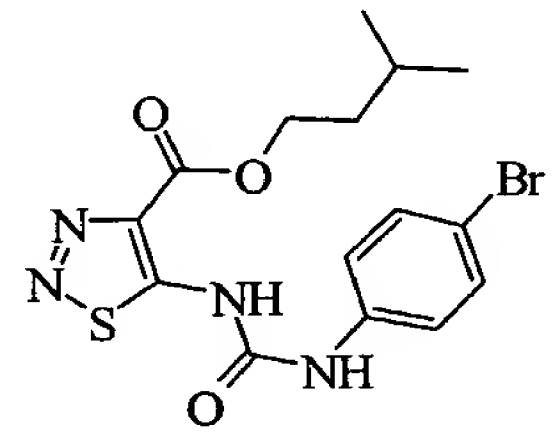
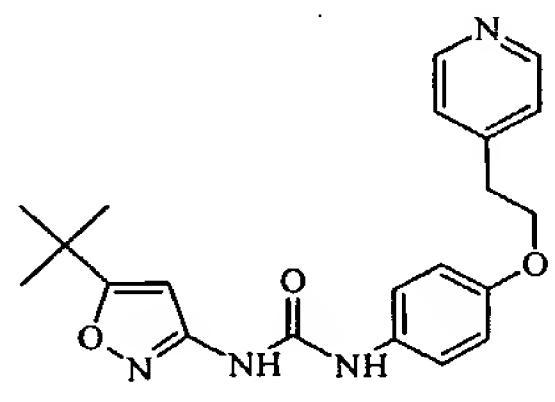
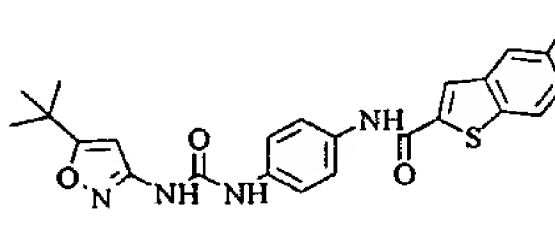
Compound Structure	Binding Assay:PDGFRB (DKIN)
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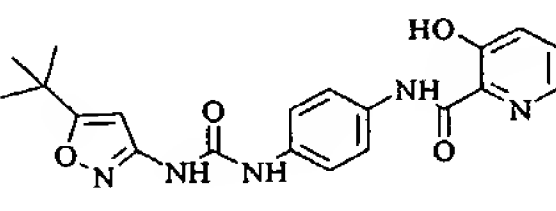
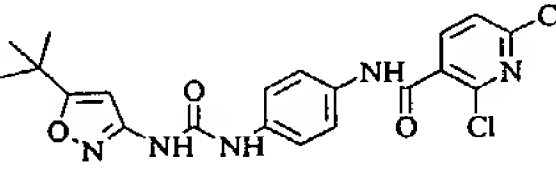
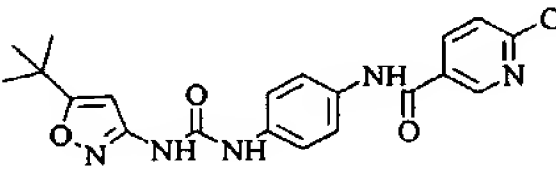
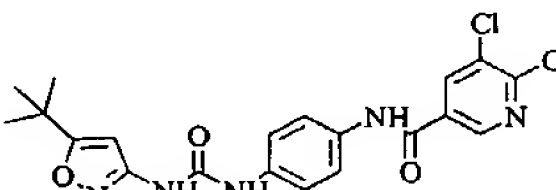
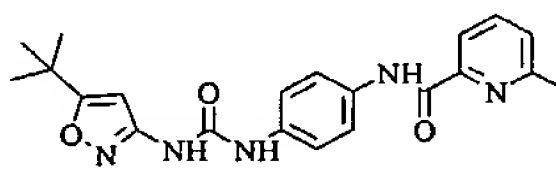
Compound Structure	Binding Assay:PDGFRB (DKIN)
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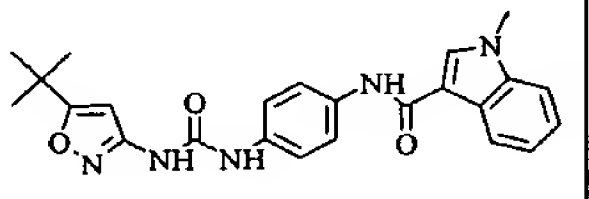
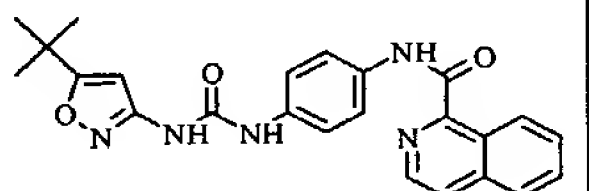
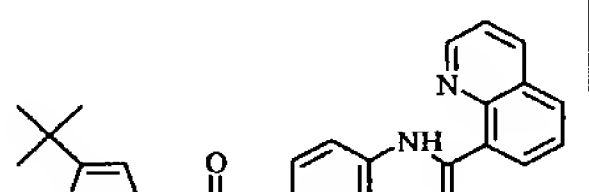
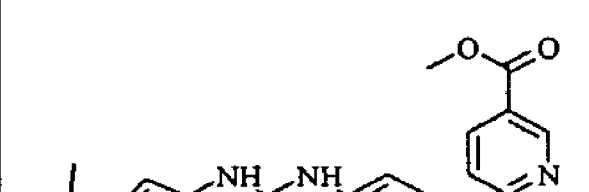

Compound Structure	Binding Assay:PDGFRB (DKIN)
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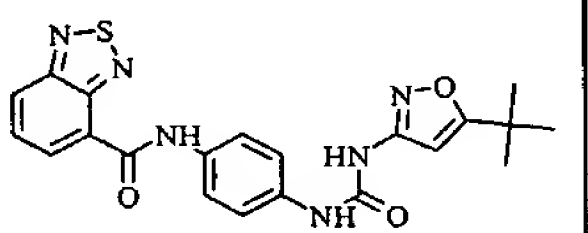
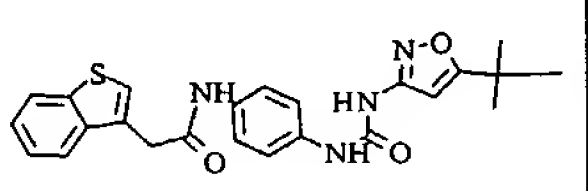
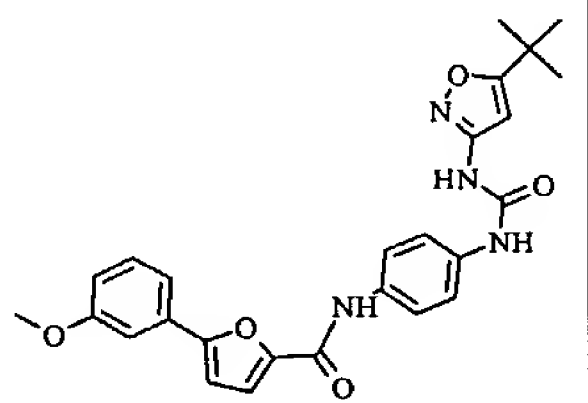
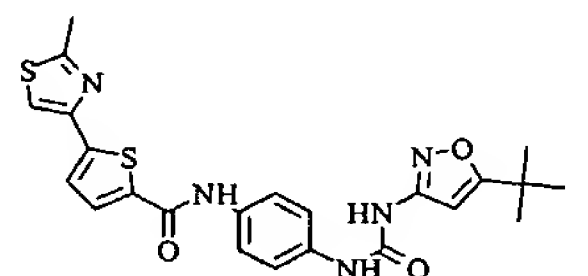
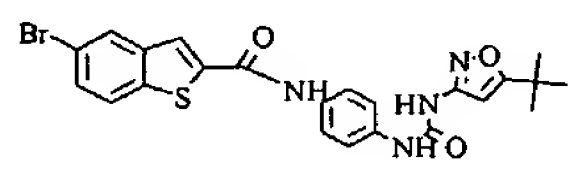
Compound Structure	Binding Assay:PDGFRB (DKIN)
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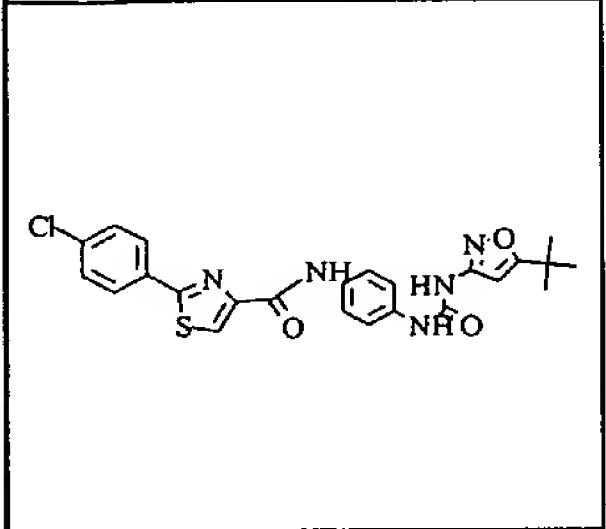
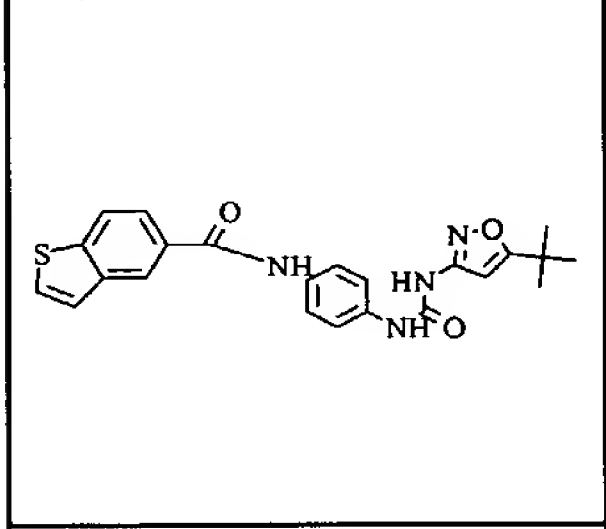
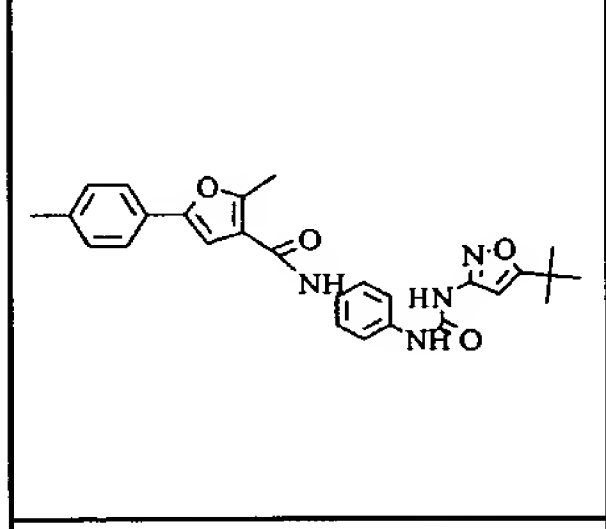
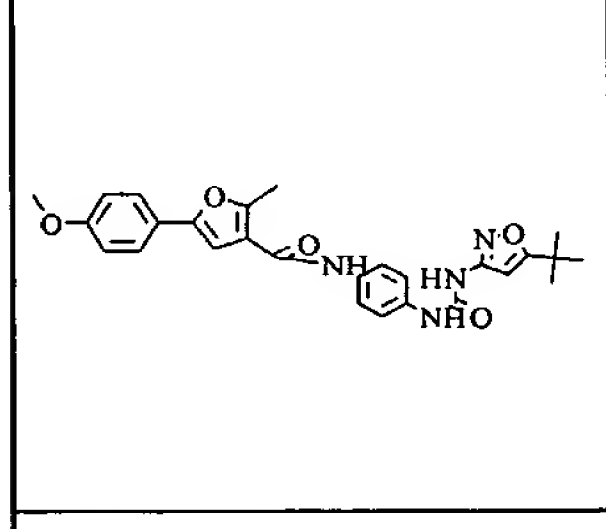
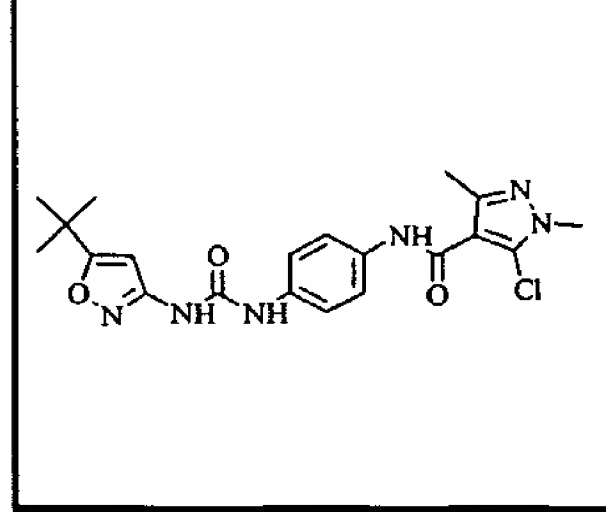
Compound Structure	Binding Assay:PDGFRB (DKIN)
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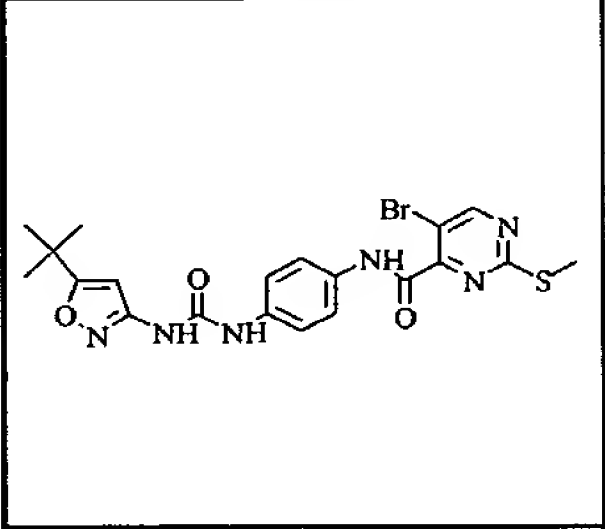
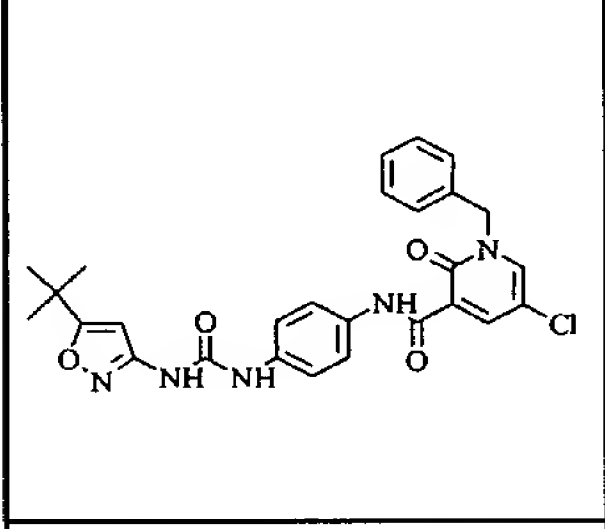
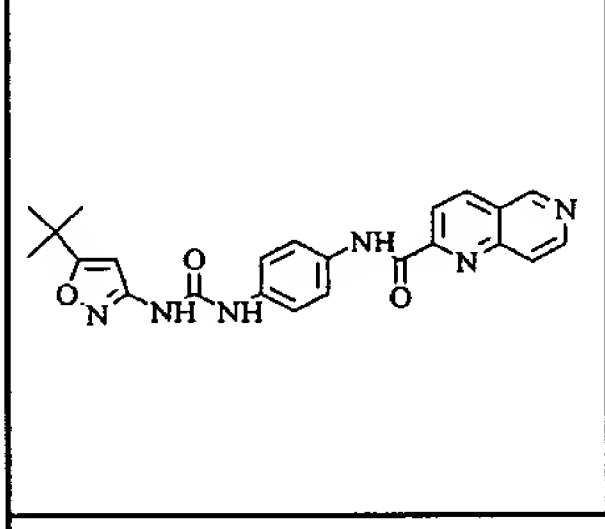
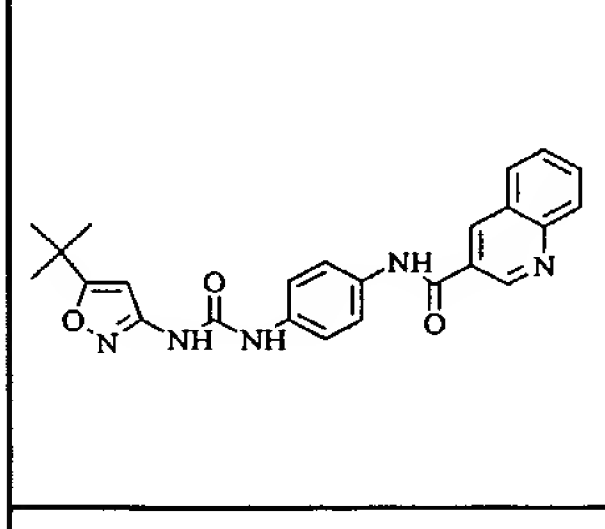
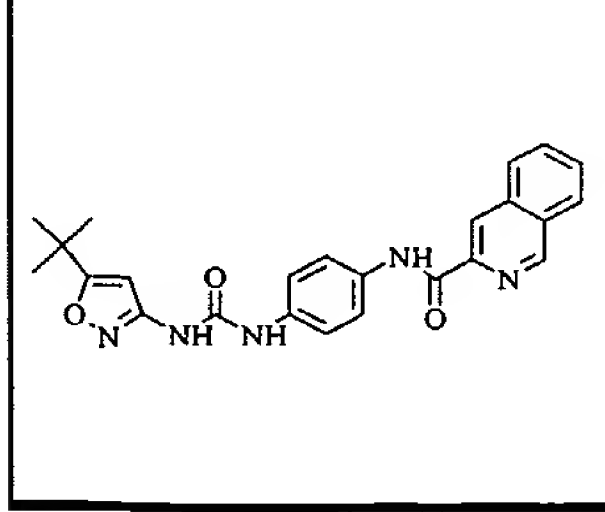
Compound Structure	Binding Assay:PDGFRB (DKIN)
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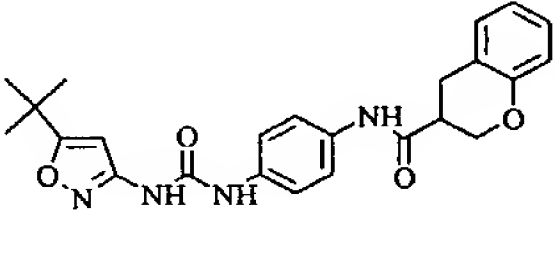
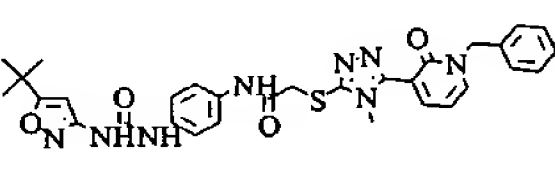
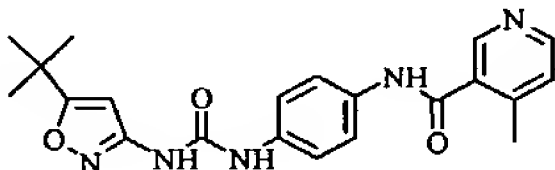
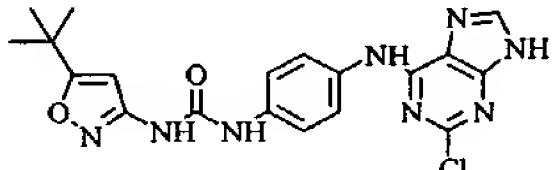
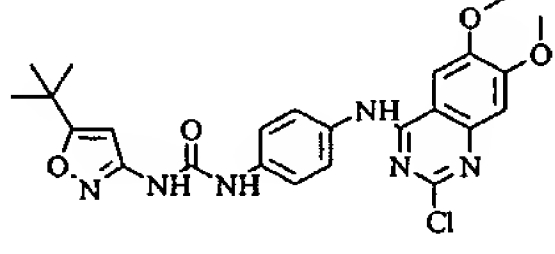
Compound Structure	Binding Assay:PDGFRB (DKIN)
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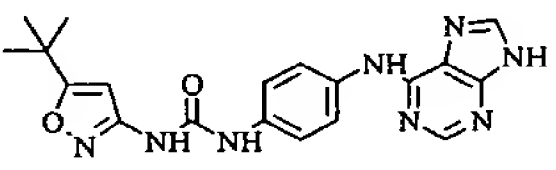
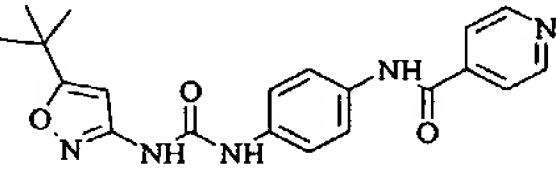
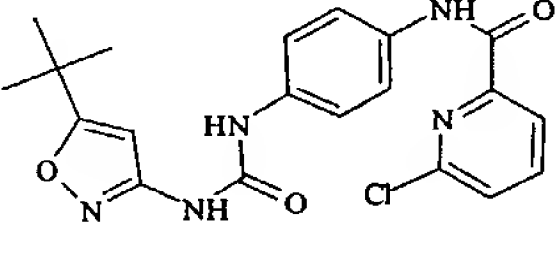
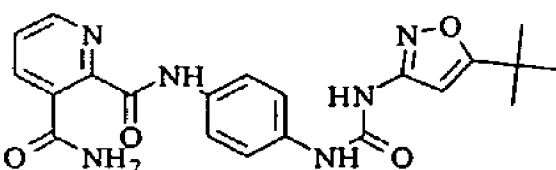
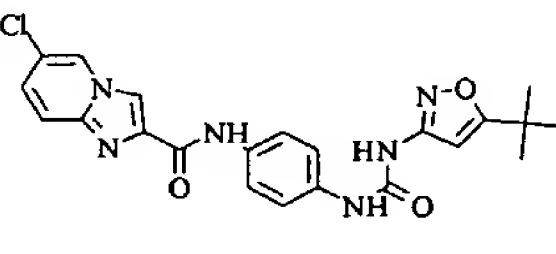
Compound Structure	Binding Assay:PDGFRB (DKIN)
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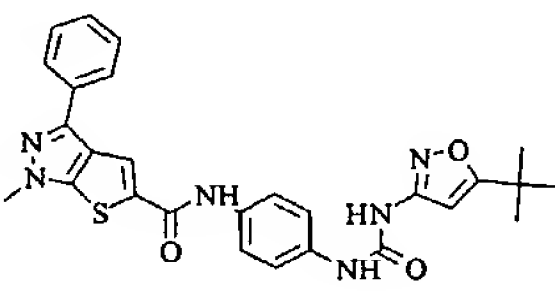
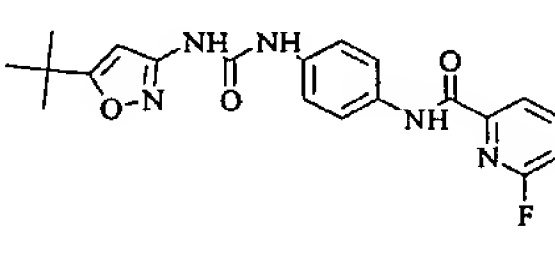
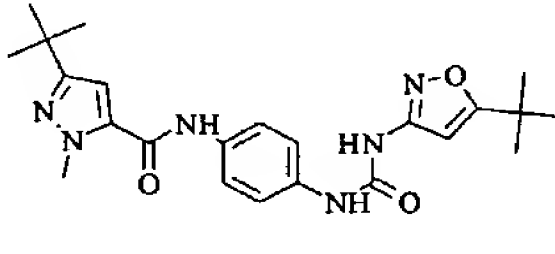
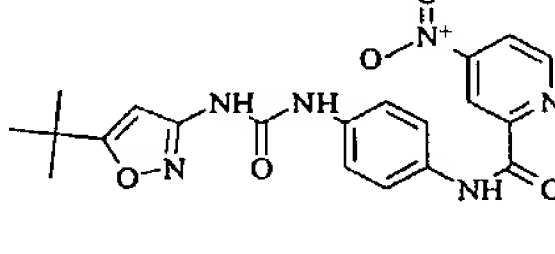
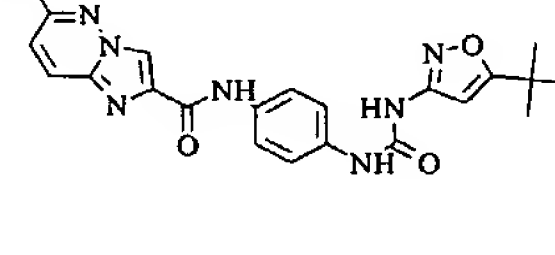
Compound Structure	Binding Assay:PDGFRB (DKIN)
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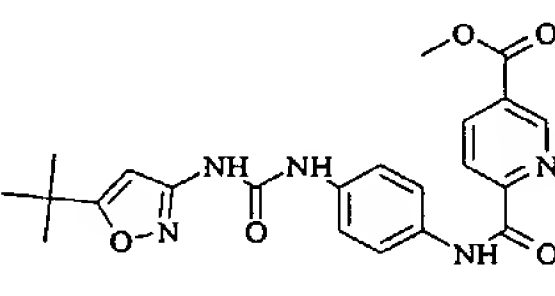
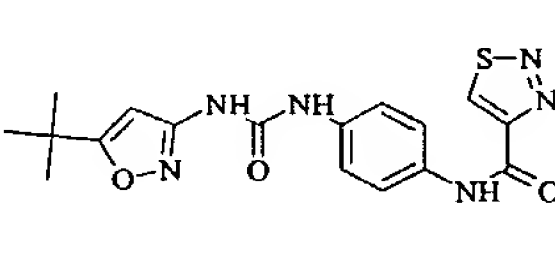
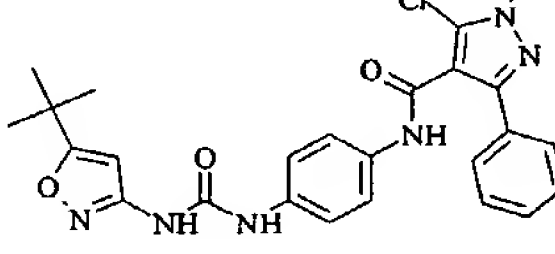
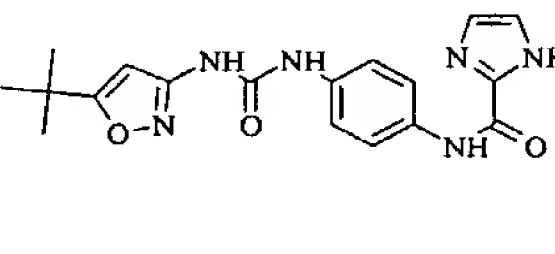
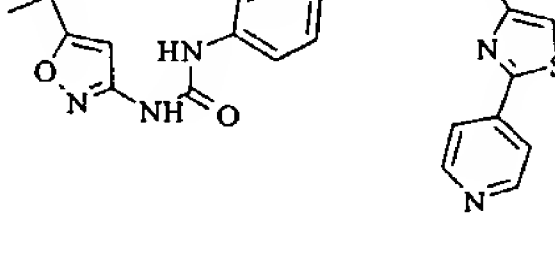
Compound Structure	Binding Assay:PDGFRB (DKIN)
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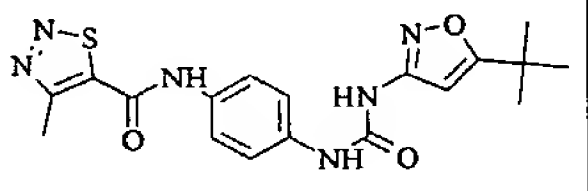
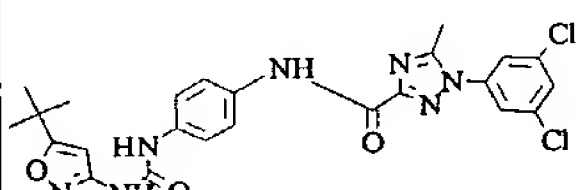
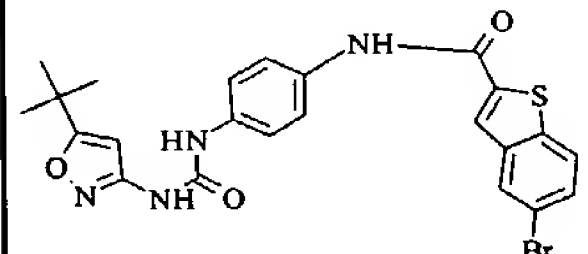
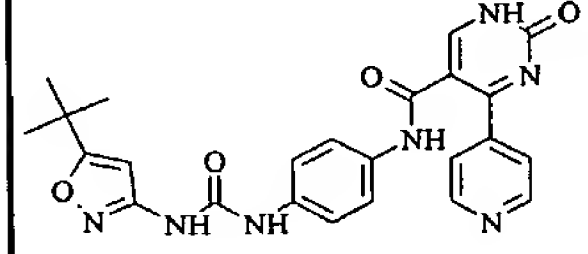
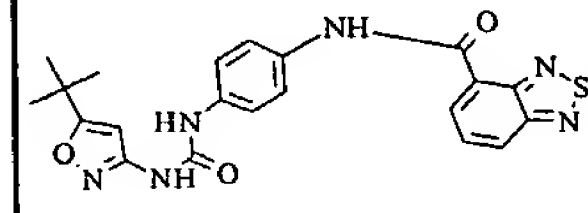
Compound Structure	Binding Assay:PDGFRB (DKIN)
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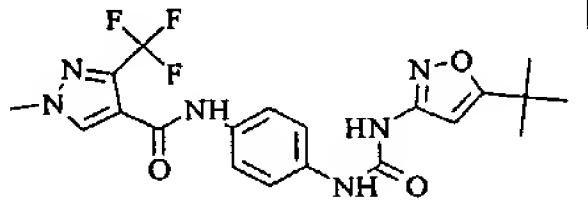
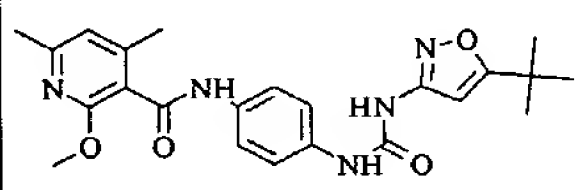
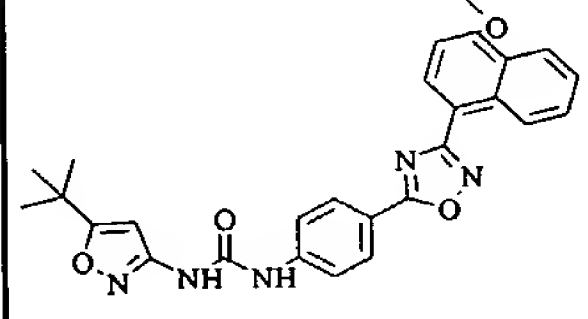
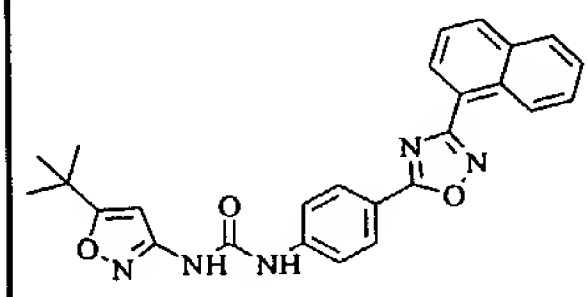
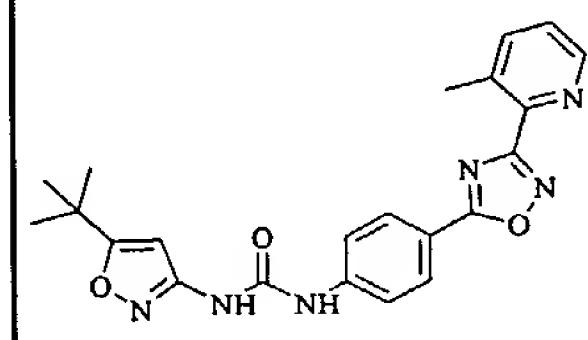
Compound Structure	Binding Assay:PDGFRB (DKIN)
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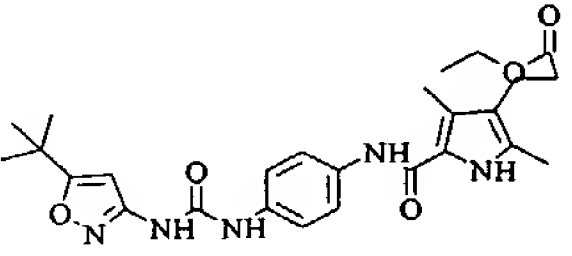
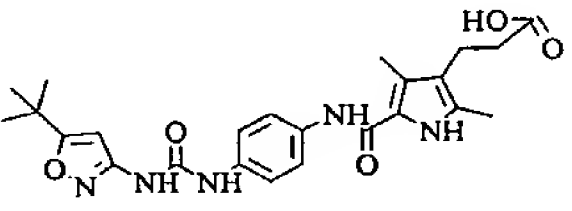
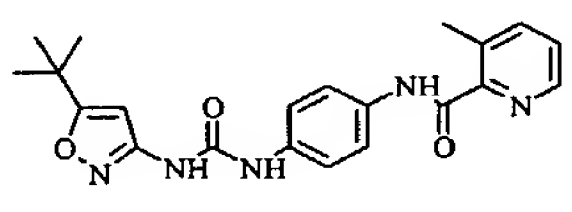
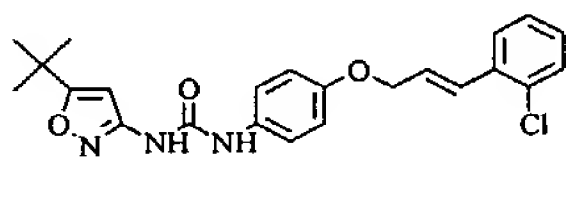
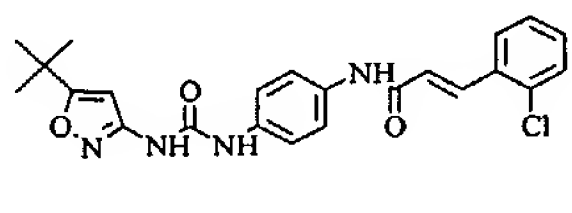
Compound Structure	Binding Assay:PDGFRB (DKIN)
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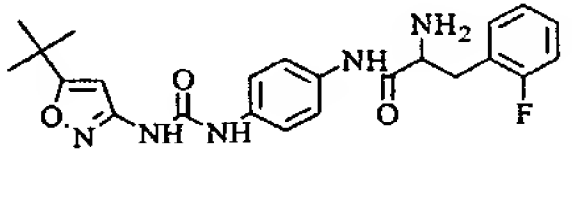
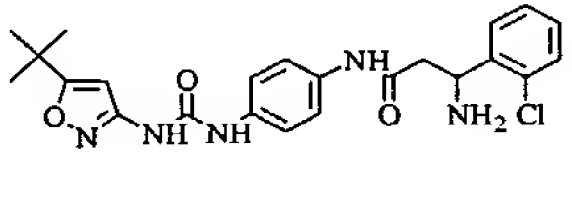
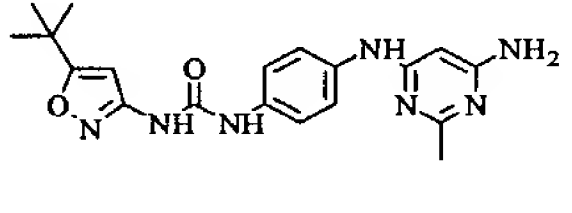
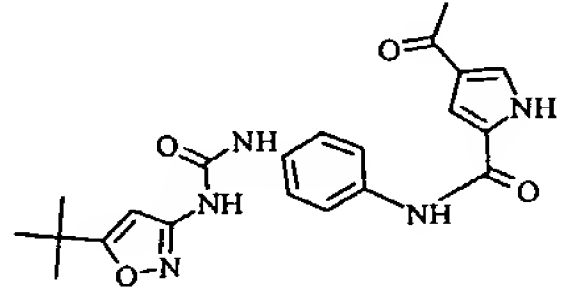
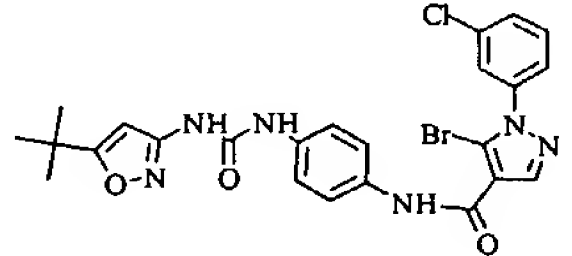
Compound Structure	Binding Assay:PDGFRB (DKIN)
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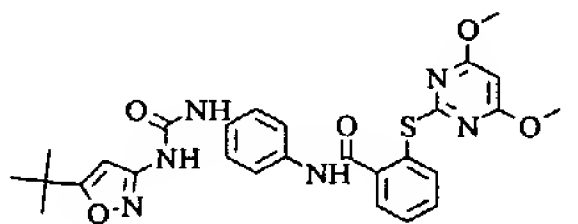
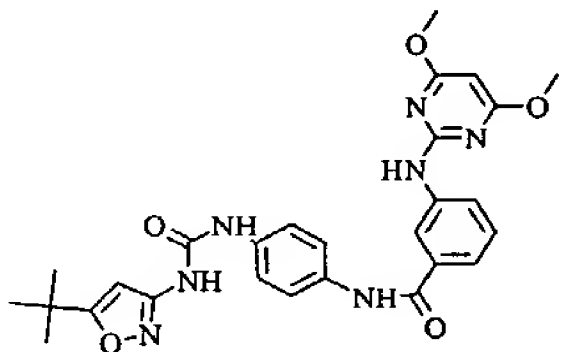
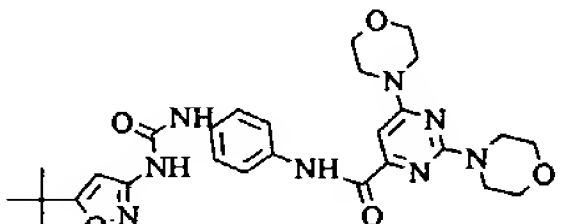
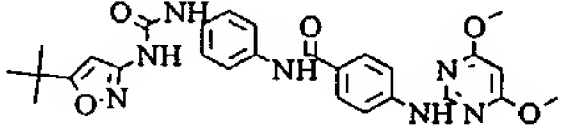
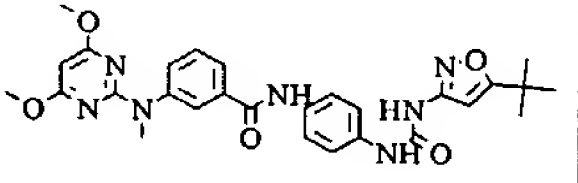
Compound Structure	Binding Assay:PDGFRB (DKIN)
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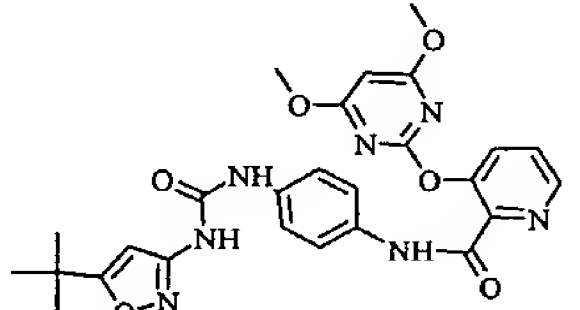
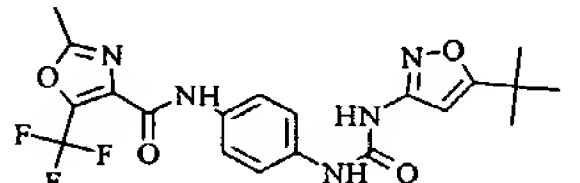
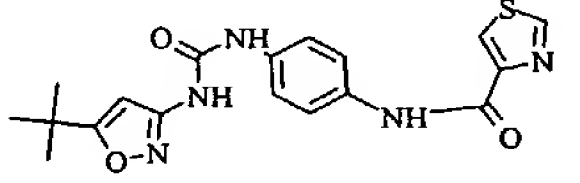
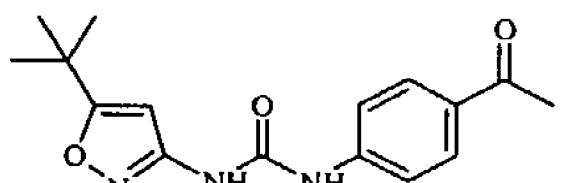
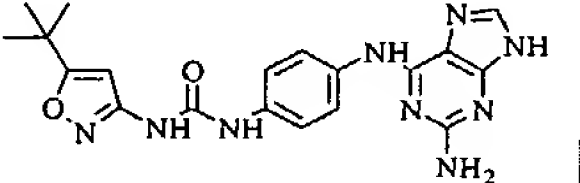
Compound Structure	Binding Assay:PDGFRB (DKIN)
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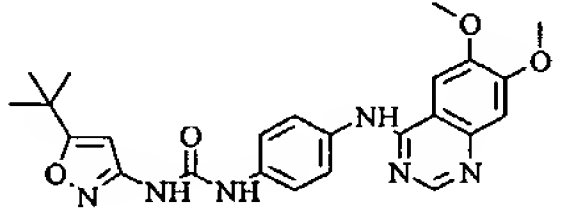
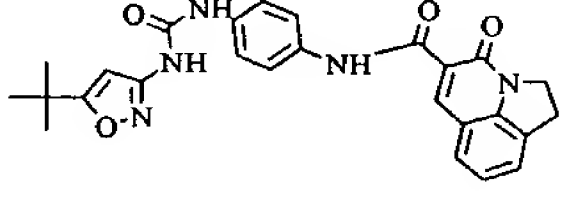
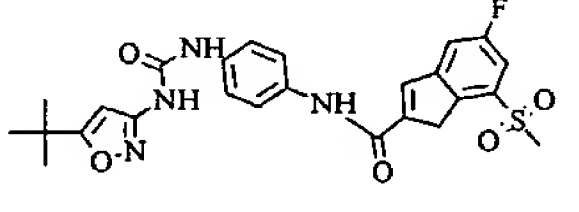
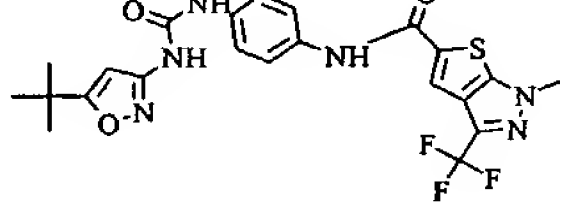
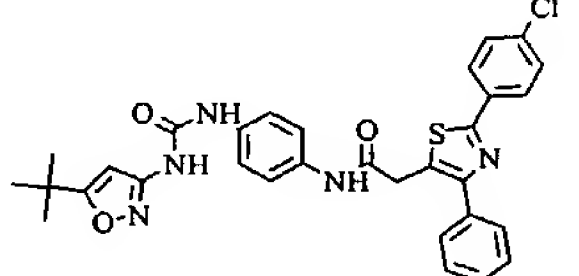
Compound Structure	Binding Assay:PDGFRB (DKIN)
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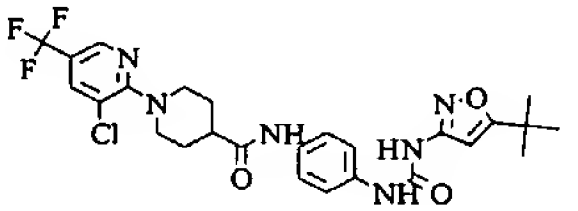
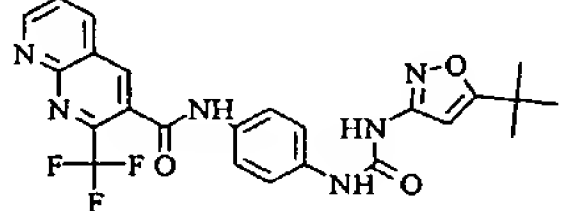
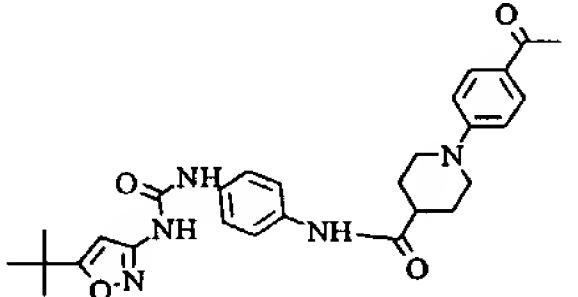
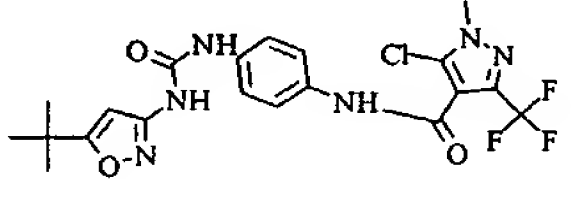
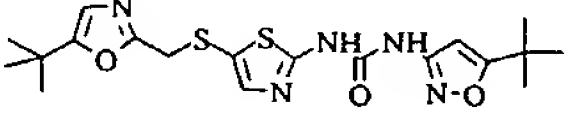
Compound Structure	Binding Assay:PDGFRB (DKIN)
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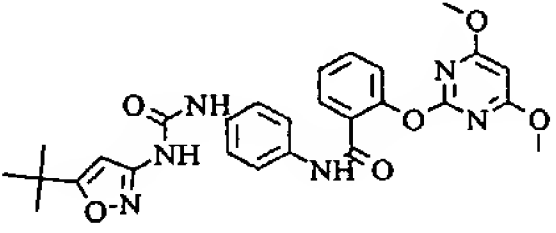
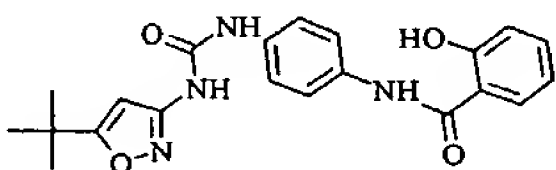
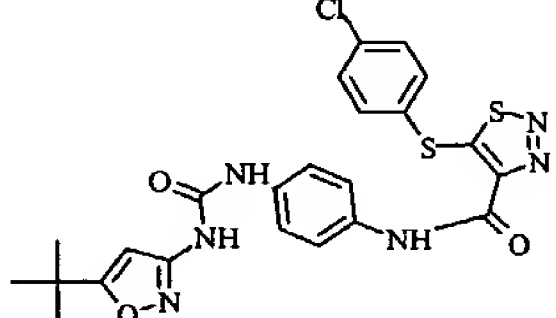
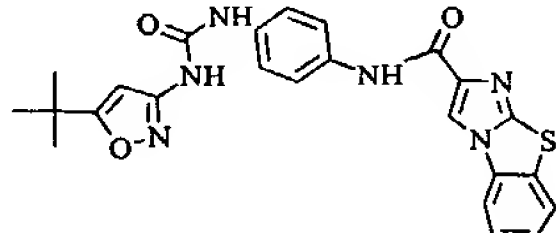
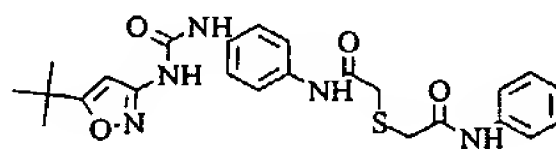
Compound Structure	Binding Assay:PDGFRB (DKIN)
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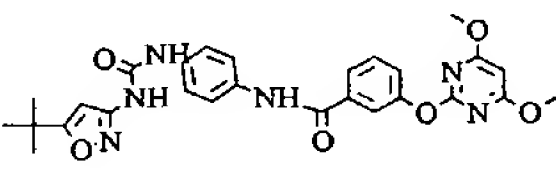
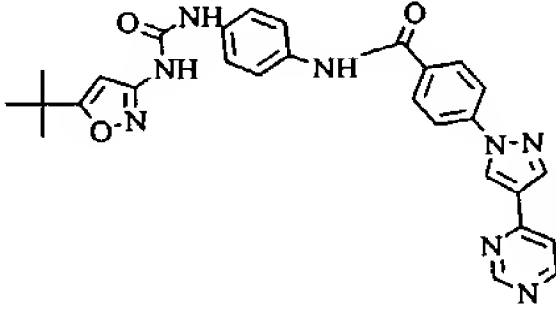
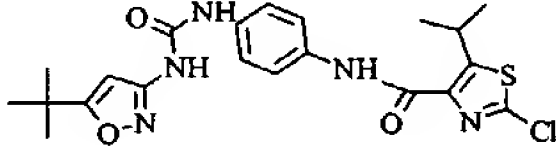
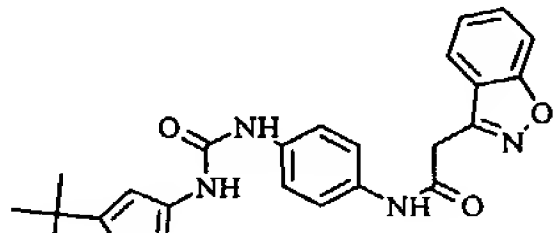
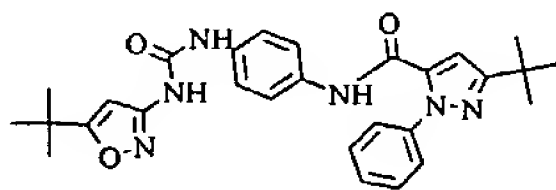
Compound Structure	Binding Assay:PDGFRB (DKIN)
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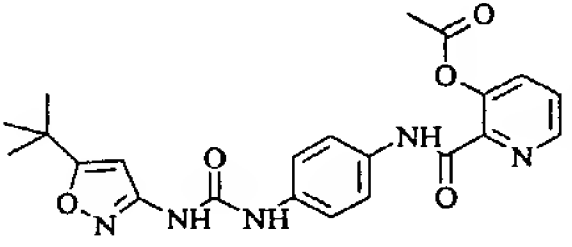
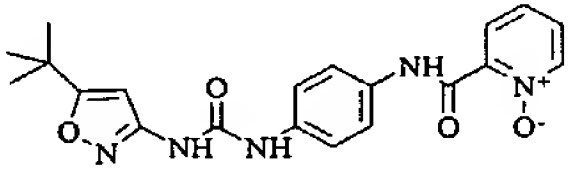
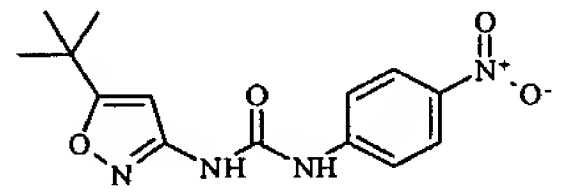
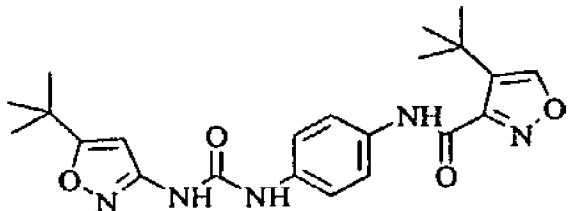
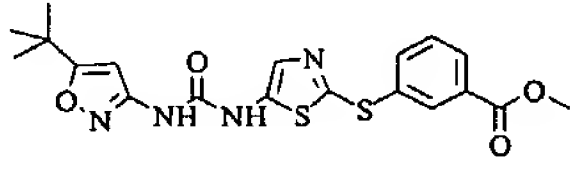
Compound Structure	Binding Assay:PDGFRB (DKIN)
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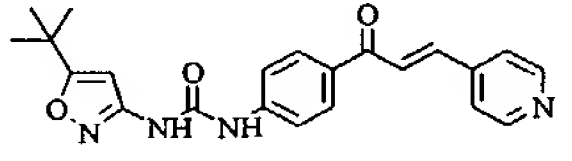
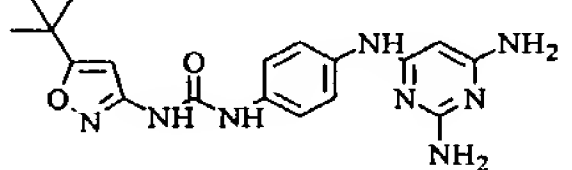
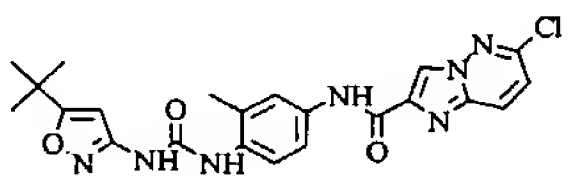
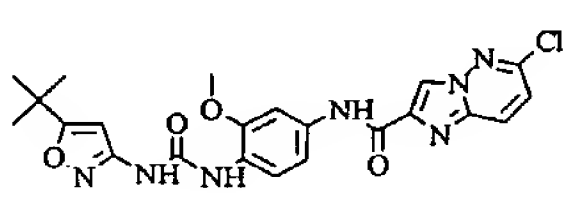
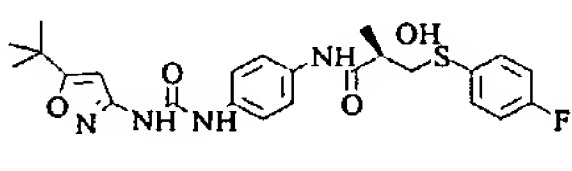
Compound Structure	Binding Assay:PDGFRB (DKIN)
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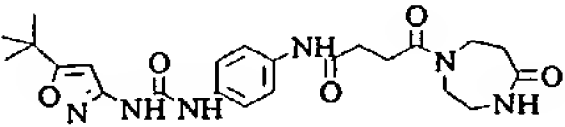
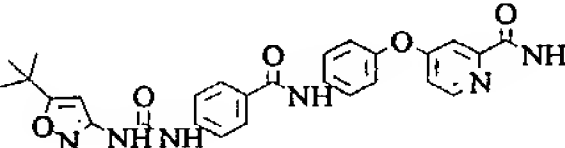
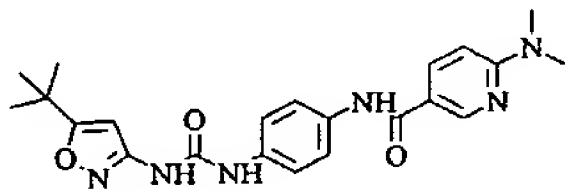
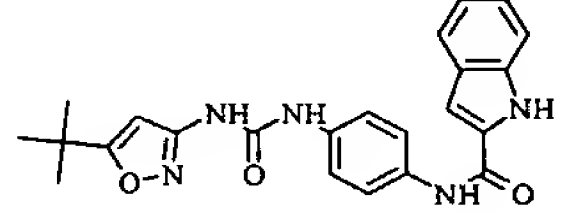
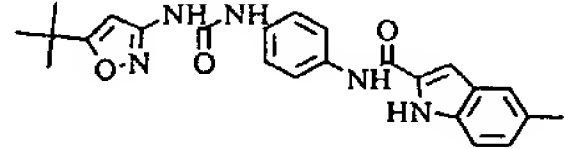
Compound Structure	Binding Assay:PDGFRB (DKIN)
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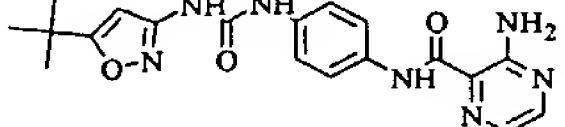
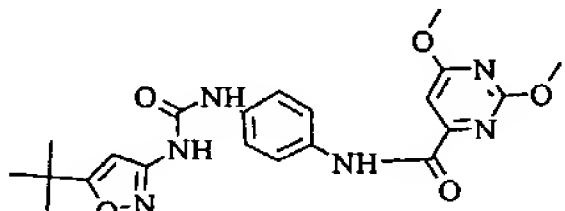
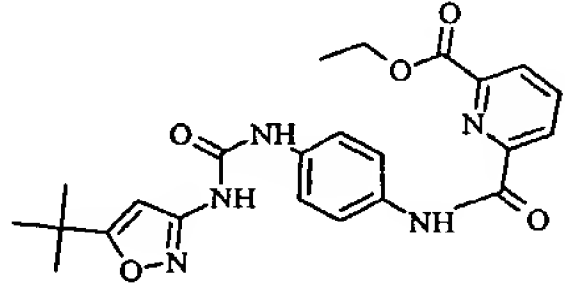
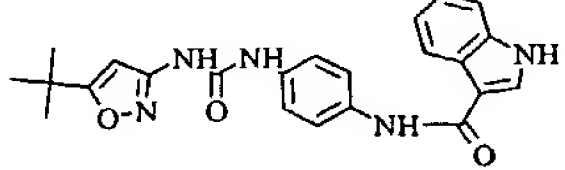
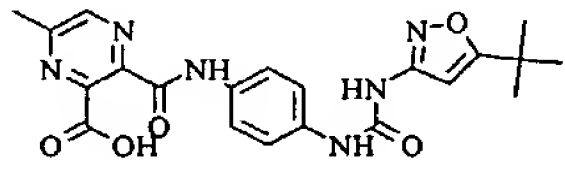
Compound Structure	Binding Assay:PDGFRB (DKIN)
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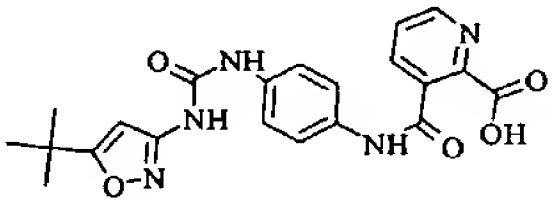
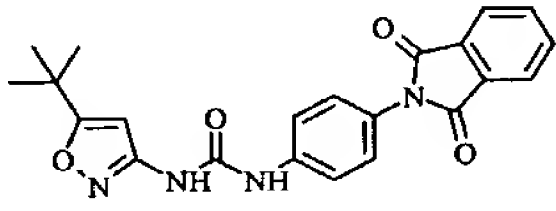
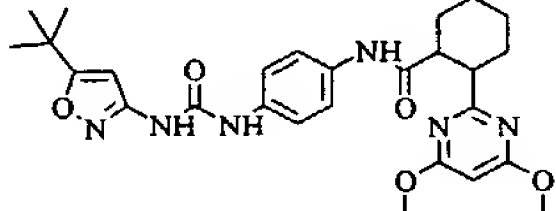
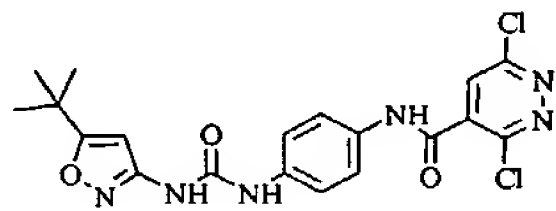
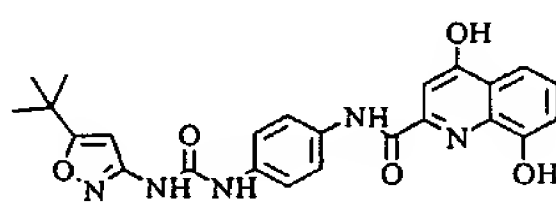
Compound Structure	Binding Assay:PDGFRB (DKIN)
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	+++
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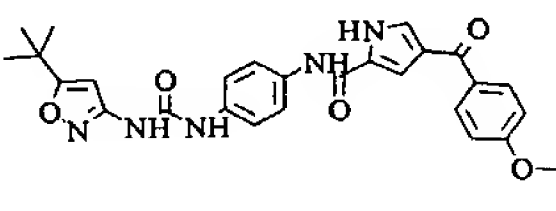
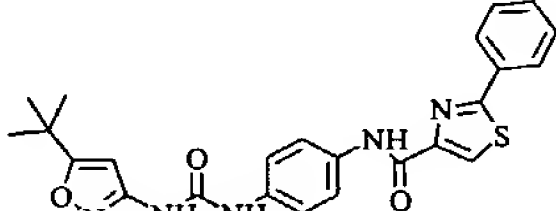
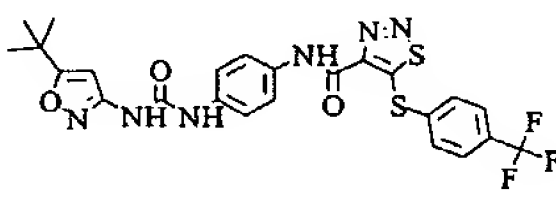
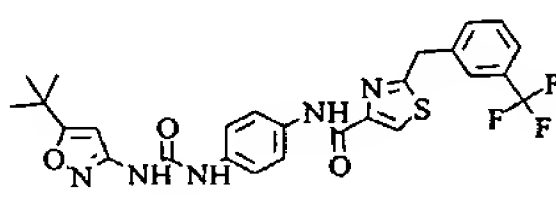
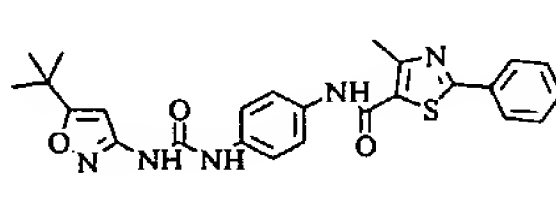
Compound Structure	Binding Assay:PDGFRB (DKIN)
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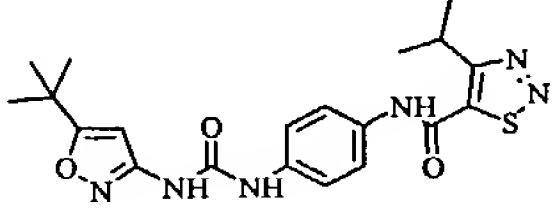
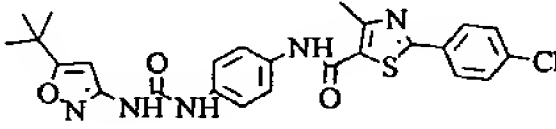
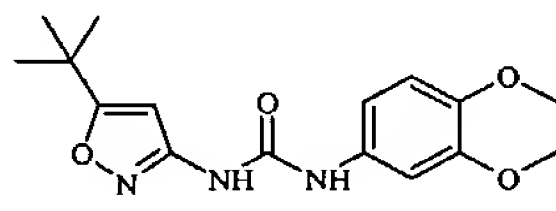
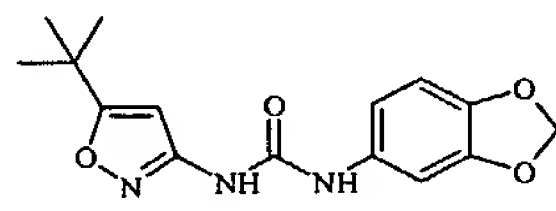
Compound Structure	Binding Assay:PDGFRB (DKIN)
	+++
	+++
	+++
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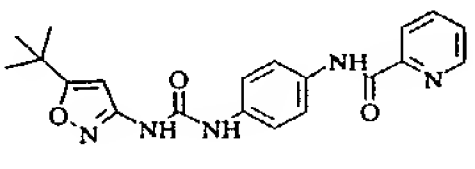
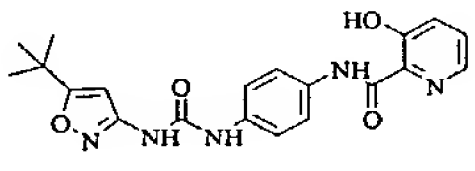
Compound Structure	Binding Assay:PDGFRB (DKIN)
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Compound Structure	Binding Assay:PDGFRB (DKIN)
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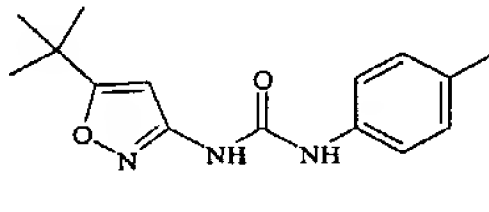
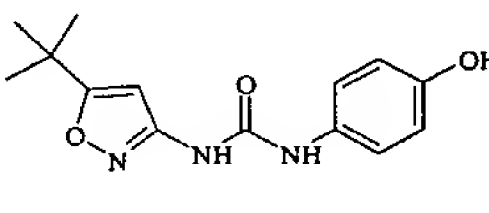
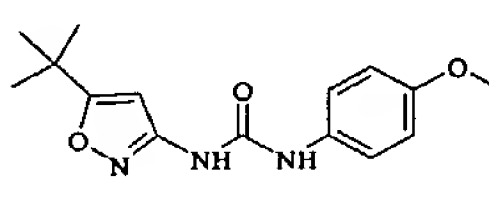
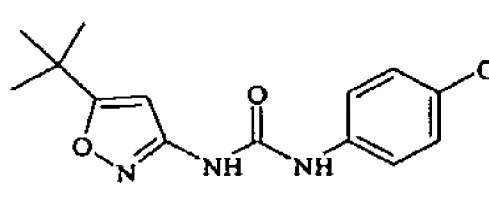
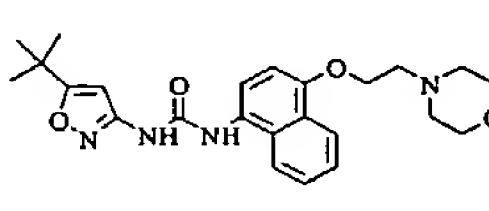
Compound Structure	Binding Assay:PDGFRB (DKIN)
	+++
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	+++
	+++
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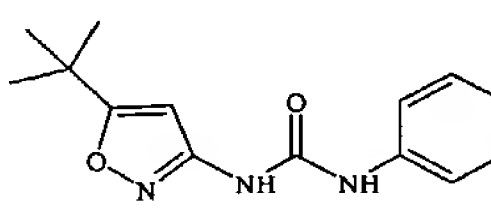
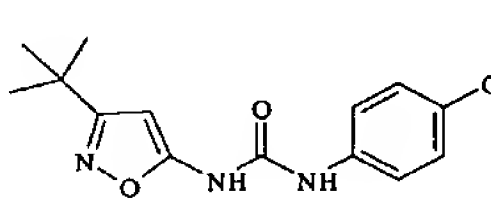
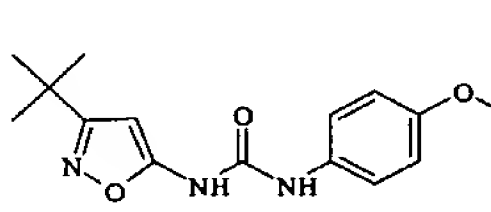
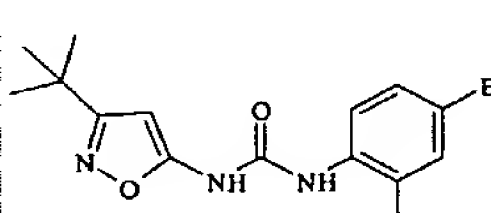
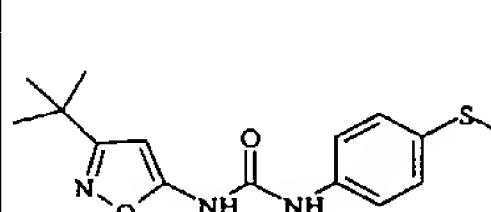
Compound Structure	Binding Assay:PDGFRB (DKIN)
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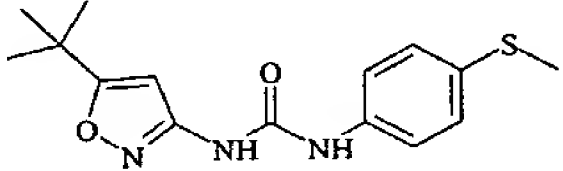
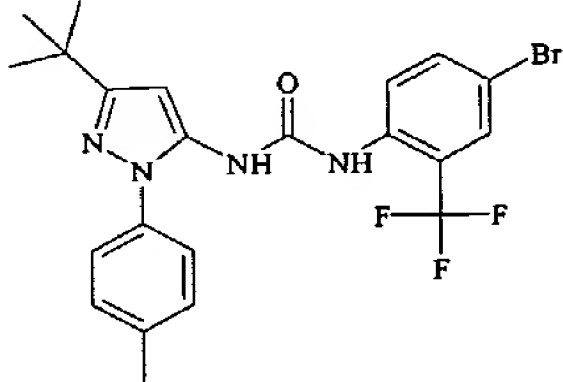
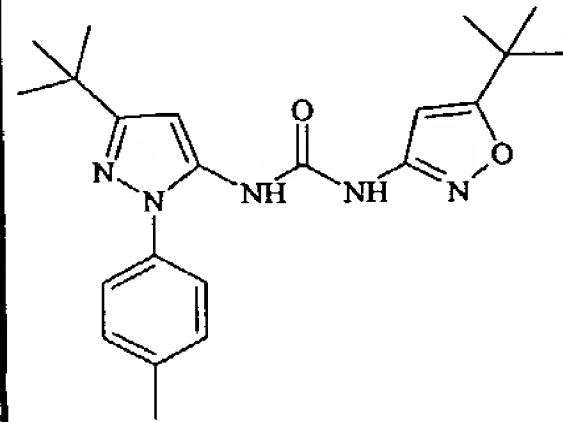
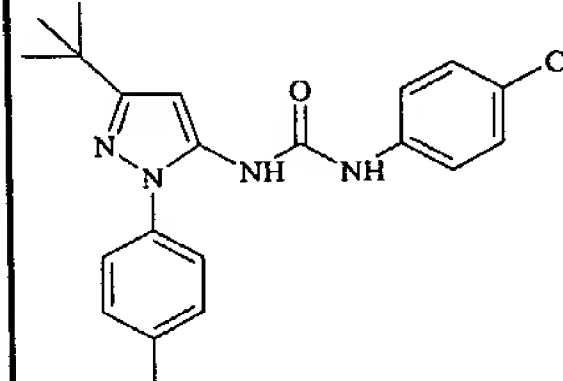
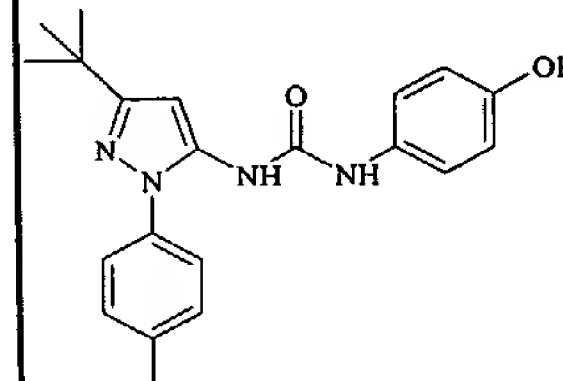
Compound Structure	Binding Assay:PDGFRB (DKIN)
	++
	+++
	++
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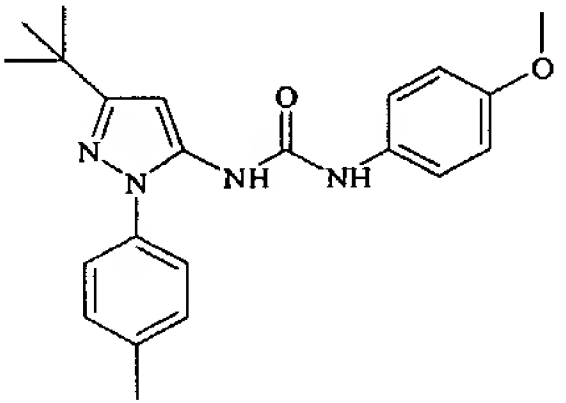
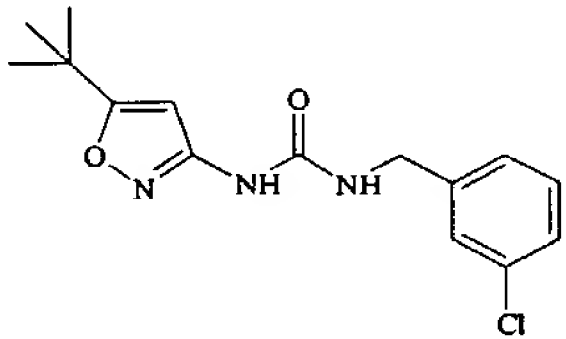
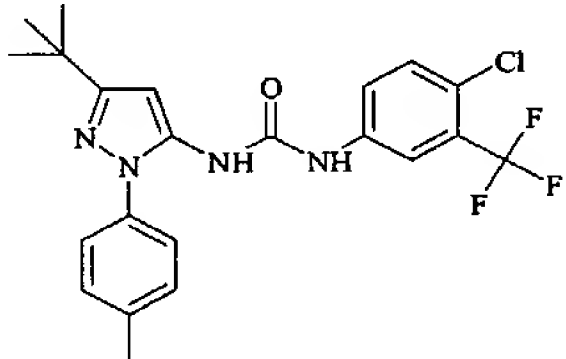
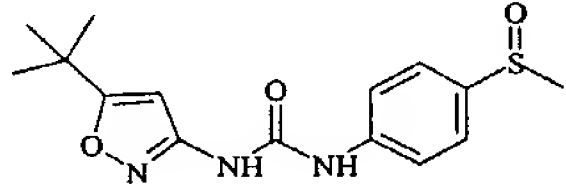
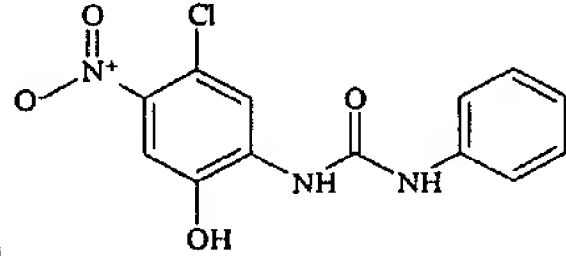
Compound Structure	Binding Assay:PDGFRB (DKIN)	Binding Assay:PD GFRB(JM plus)	Binding Assay:PD GFRB(JM minus)
	+++++	+++++	+++++
	+++++	+++++	+++++

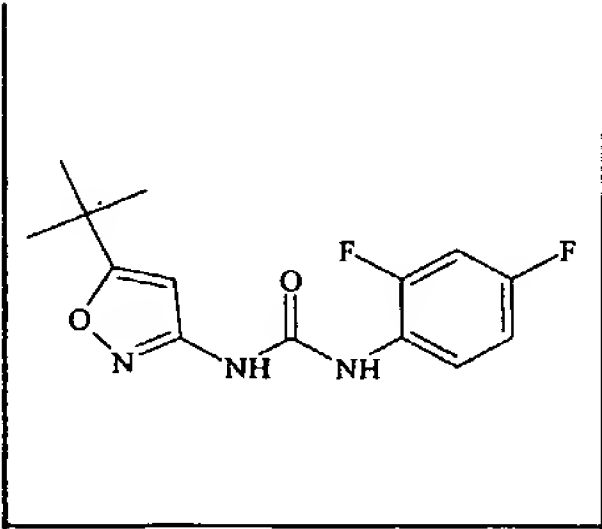
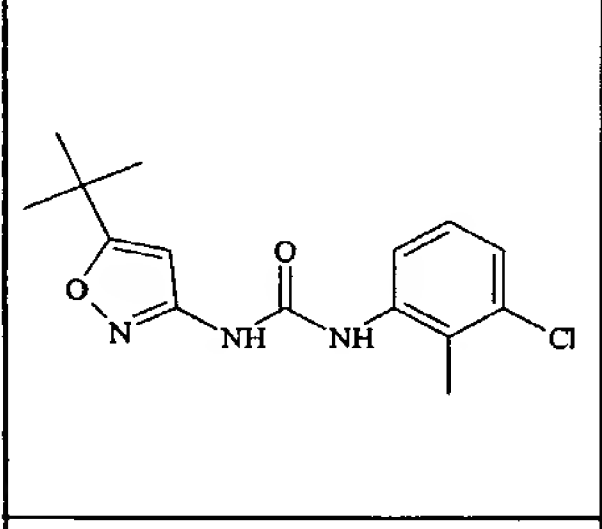
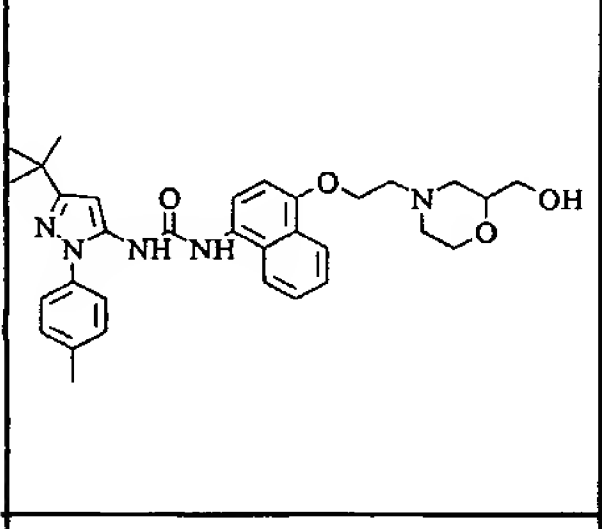
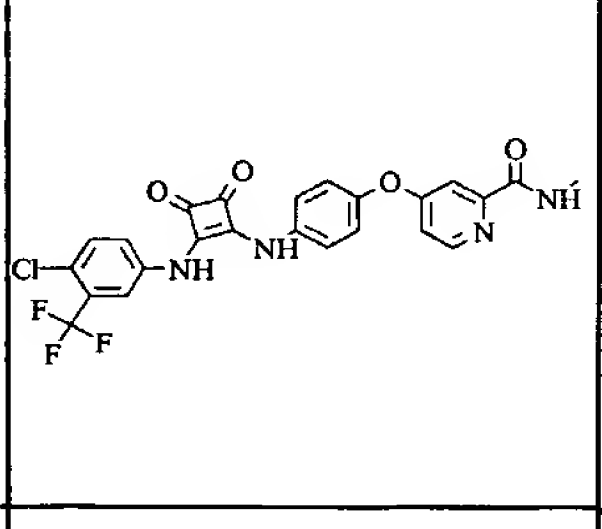
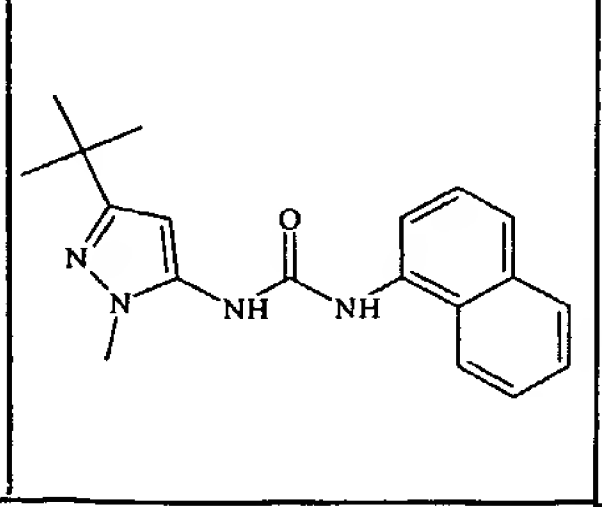
Binding Constant (K_d) Measurements for Small-Molecule- p38 Interactions

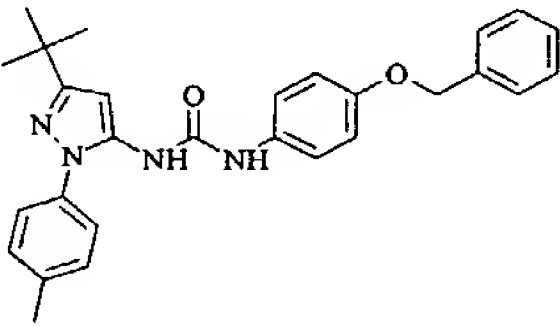
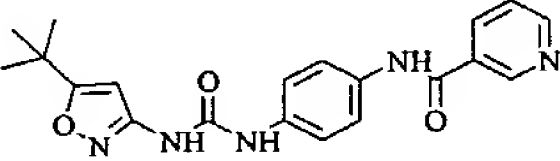
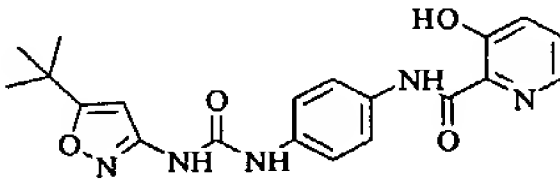
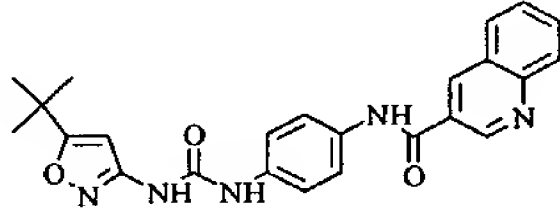
Compound Structure	Binding Assay:p38-alpha(FKIN)
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	++
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	+++++

Compound Structure	Binding Assay:p38-alpha(FKIN)
	++
	++
	++
	+++
	++

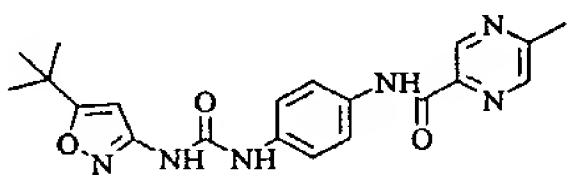
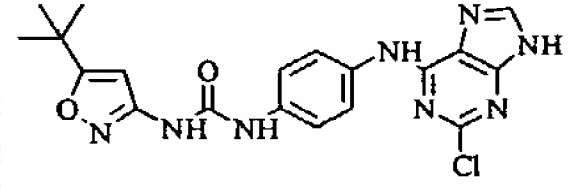
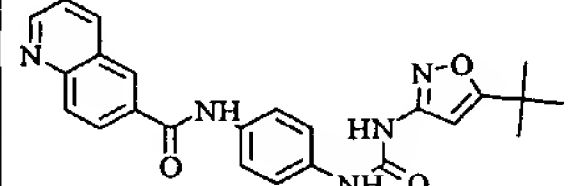
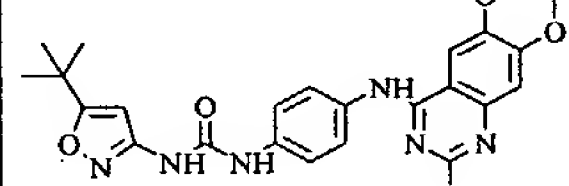
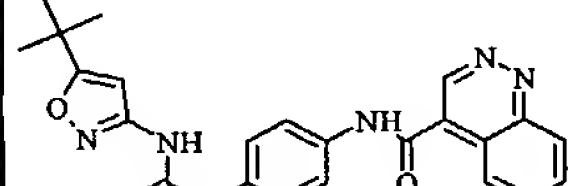
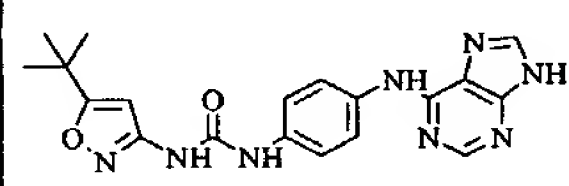
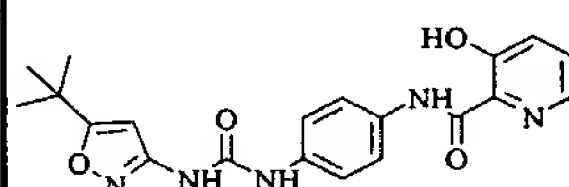
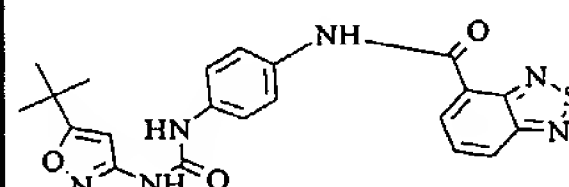
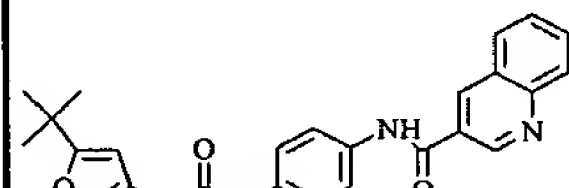
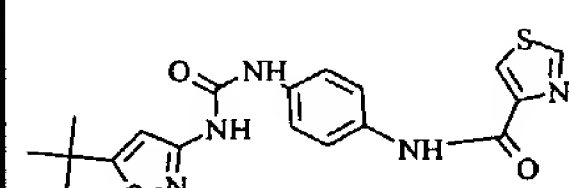
Compound Structure	Binding Assay:p38-alpha(FKIN)
	++
	+++
	+++
	++++
	+++

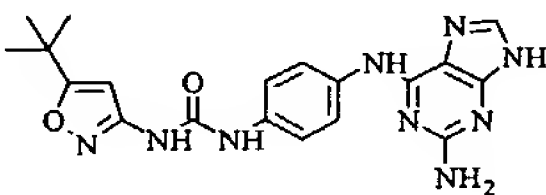
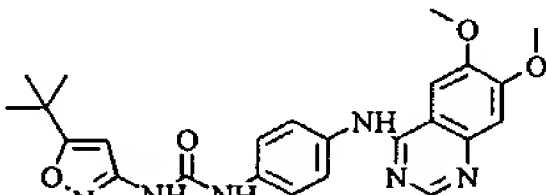
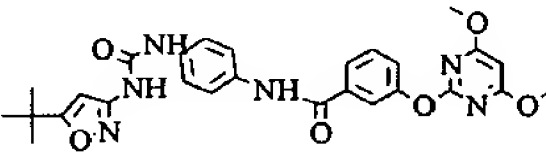
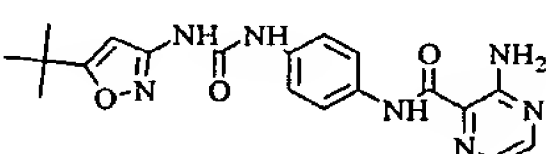
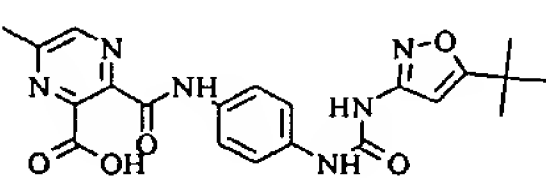
Compound Structure	Binding Assay:p38-alpha(FKIN)
	+++
	+++
	+++
	++
	+++

Compound Structure	Binding Assay:p38-alpha(FKIN)
	++
	+++
	++++
	+++
	+++

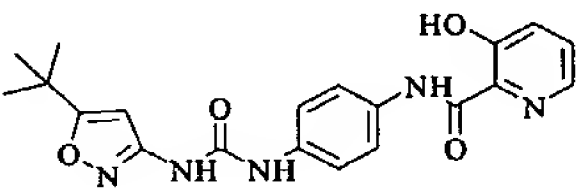
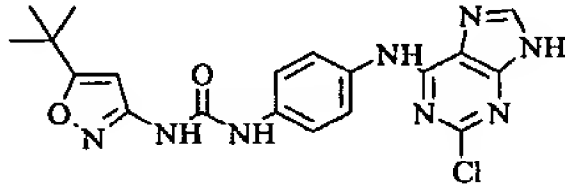
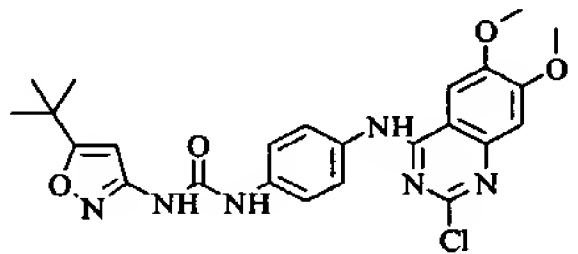
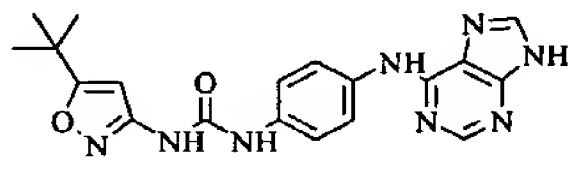
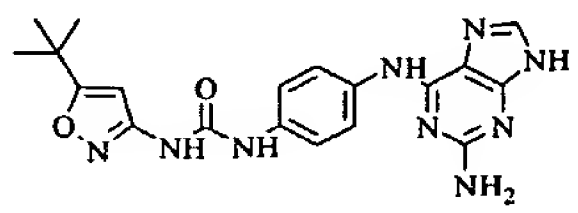
Compound Structure	Binding Assay:p38-alpha(FKIN)
	+++
	+++
	ND
	++

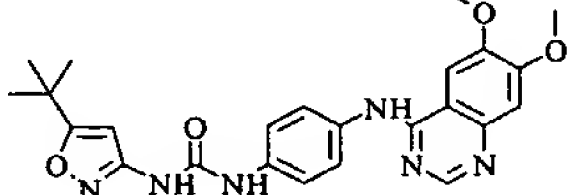
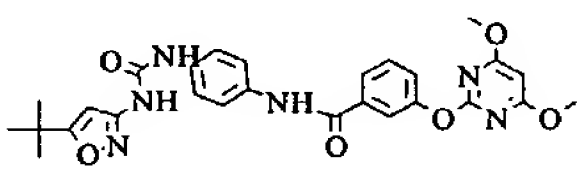
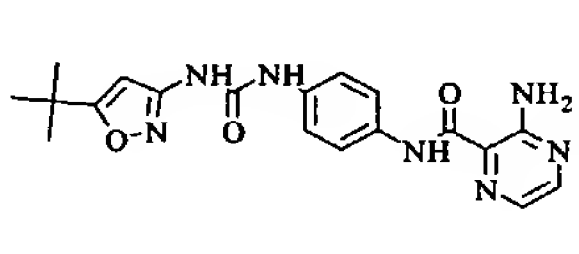
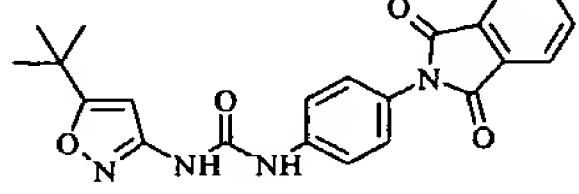
Binding Constant (K_d) Measurements for Small-Molecule- MKNK2 Interactions

Compound Structure	Binding Assay:MKNK2(DKIN)	Compound Structure	Binding Assay:MKNK2(DKIN)
	+++		++
	++		++
	++++		++++
	++++		++
	++		+++

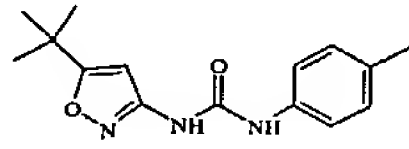
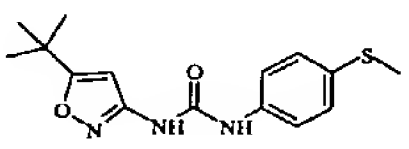
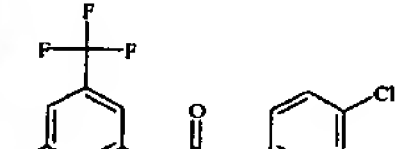
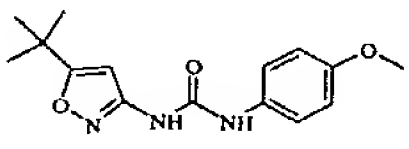
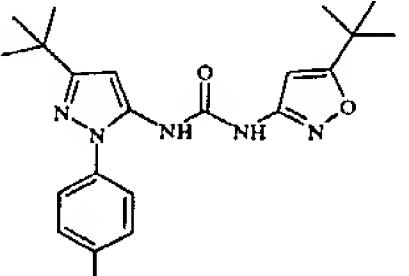
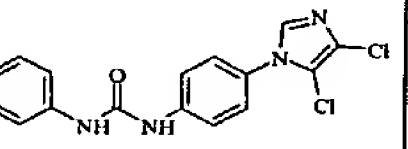
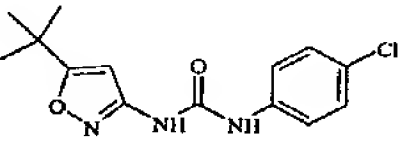
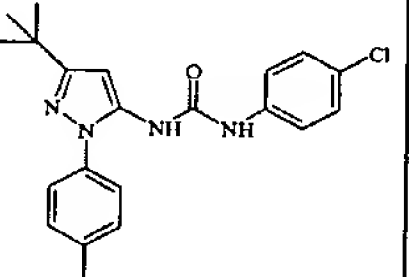
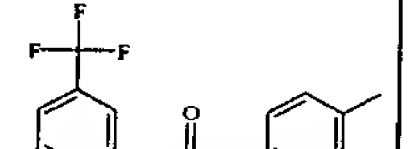
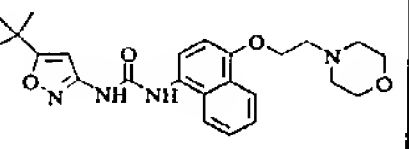
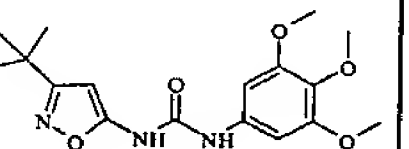

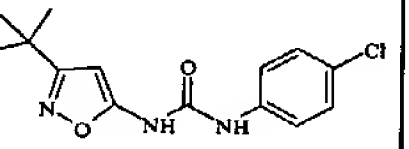
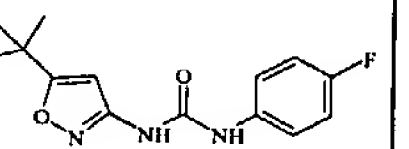
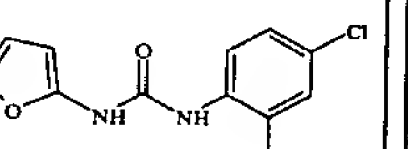
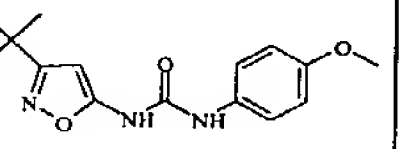
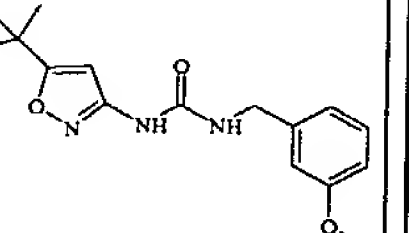
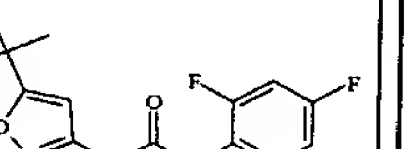
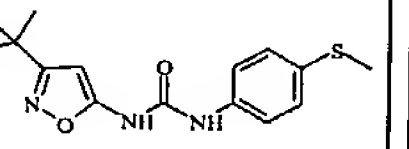
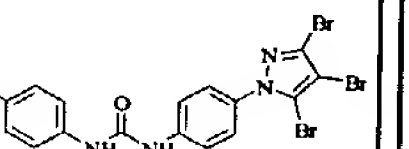
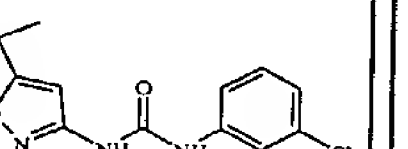
Compound Structure	Binding Assay: MKNK2(DKIN)
	+++++
	+++++
	+++
	+++
	++

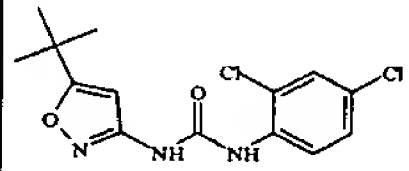
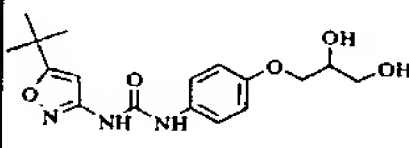
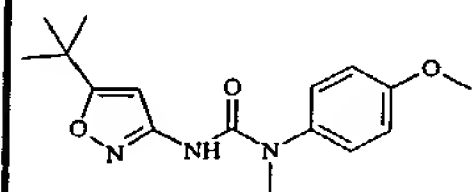
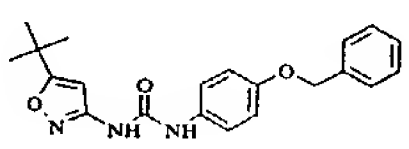
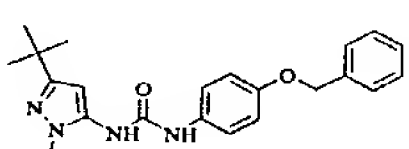
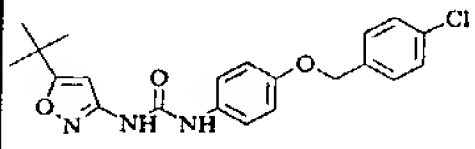
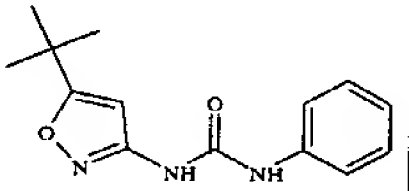
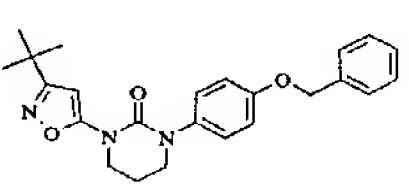
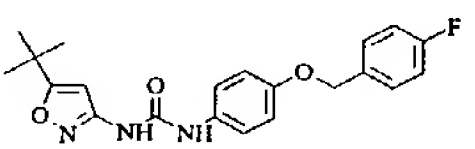
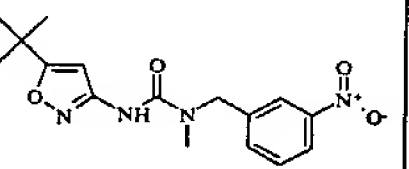
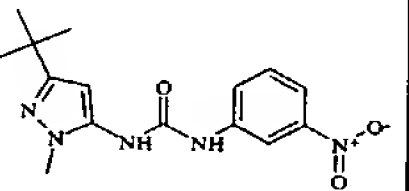
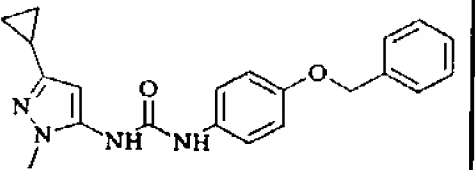
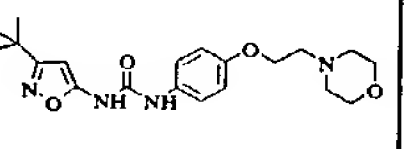
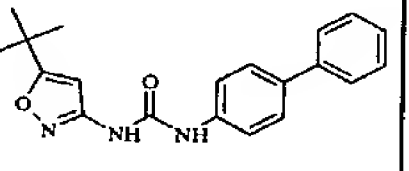
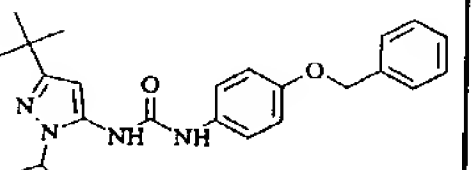
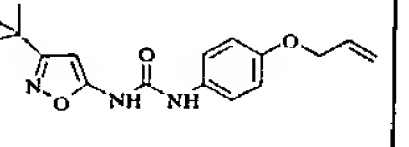
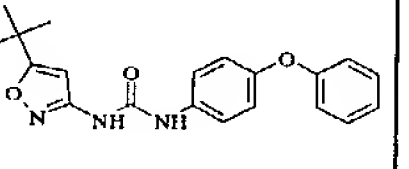
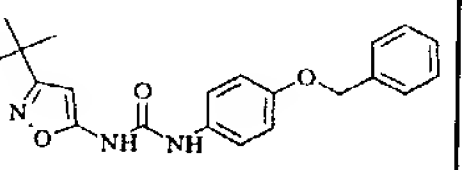
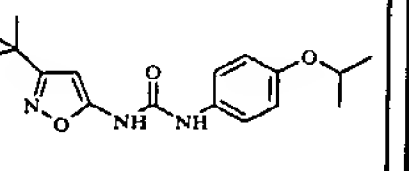
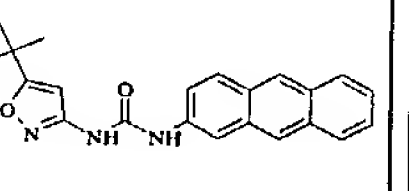
Binding Constant (K_d) Measurements for Small-Molecule- STK10 Interactions

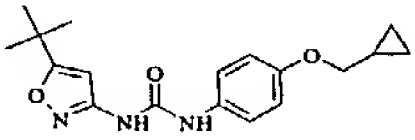
Compound Structure	Binding Assay:STK10(DKIN)
	+++
	+++
	++++
	++++
	+++

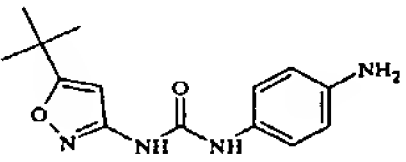
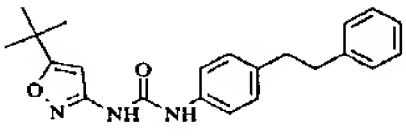
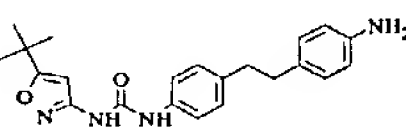
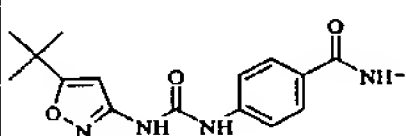
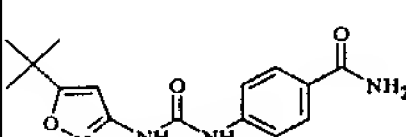
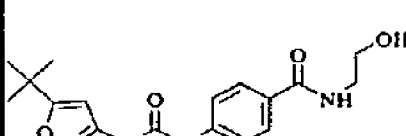
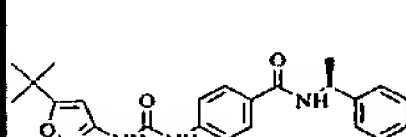
Compound Structure	Binding Assay:STK10(DKIN)
	++++
	++
	+++
	++++

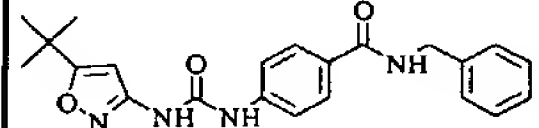
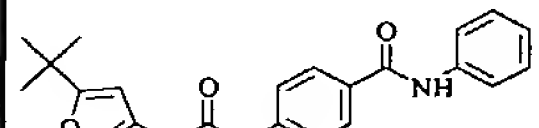



Binding Constant (K_d) Measurements for Small-Molecule- c-kit Interactions

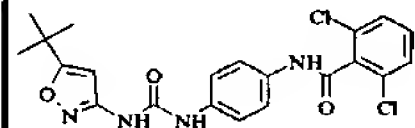
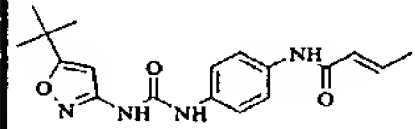
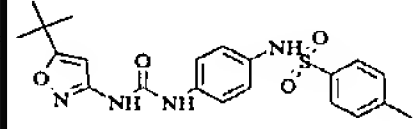
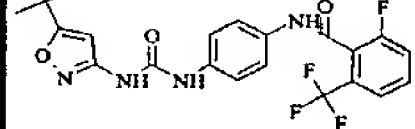
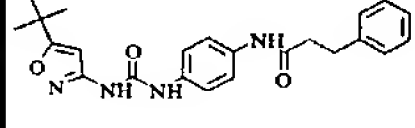
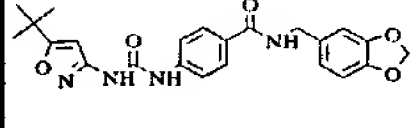
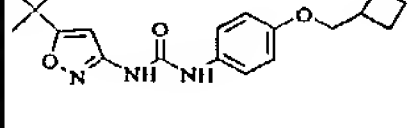
Compound Structure	Binding Assay:KIT (DKIN)	Compound Structure	Binding Assay:KIT (DKIN)	Compound Structure	Binding Assay:KIT (DKIN)
	+++		+++		+++
	++		+		++
	+++		++		+++
	++		+++		+++
	+++		++		++
	+++		++		+++
	+++		+++		++

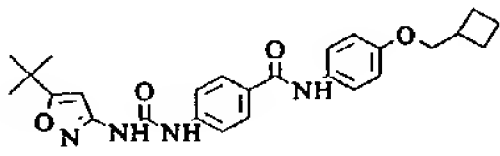
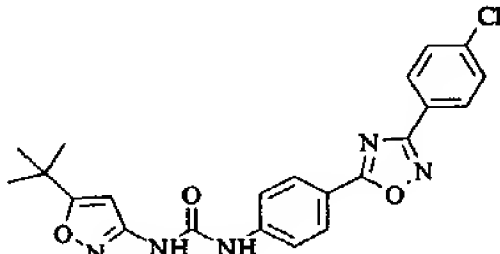
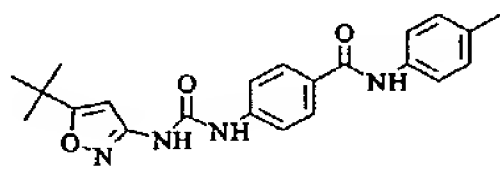
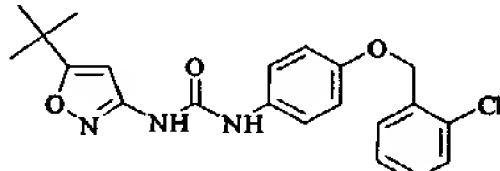
Compound Structure	Binding Assay:KIT (DKIN)	Compound Structure	Binding Assay:KIT (DKIN)	Compound Structure	Binding Assay:KIT (DKIN)
	+++		+++		+++
	++++		+++		++++
	+++		++		++++
	++		+		+
	++		+++		+
	++++		+++		+++
	++++		++		

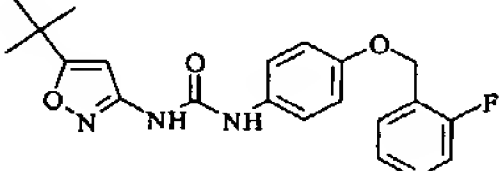
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)
	++++	++++	+++	++

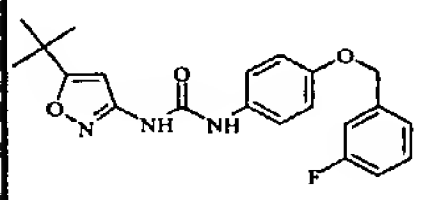
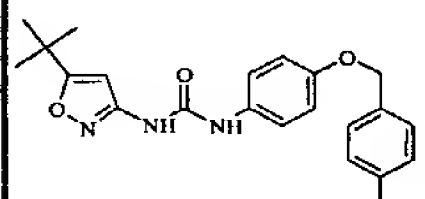
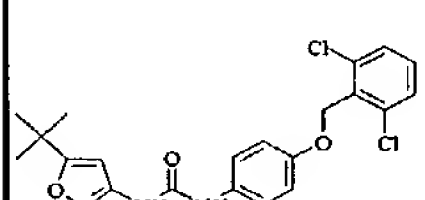
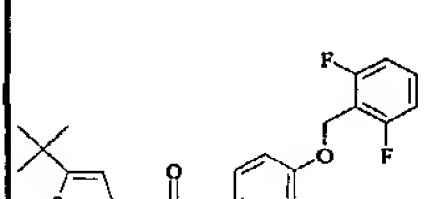
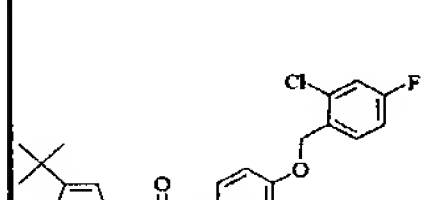
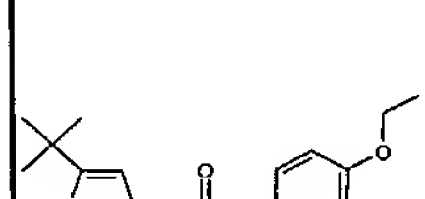
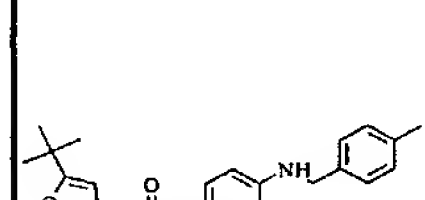
Compound Structure	Binding Assay:KIT (DKIN)
	++
	+++
	++++
	+++
	+++
	+++
	+++

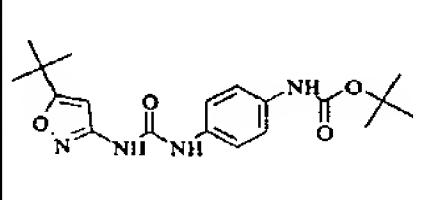
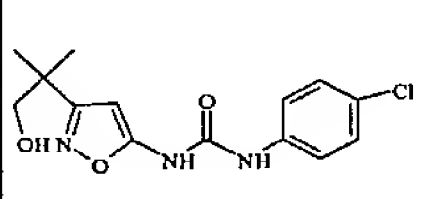
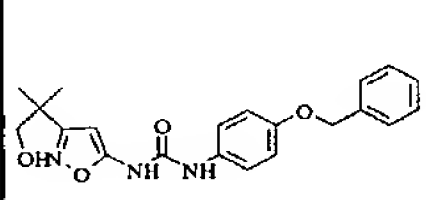
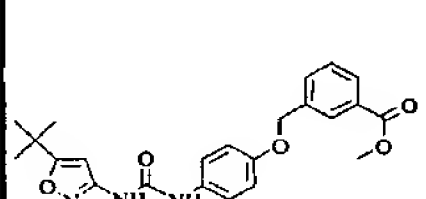
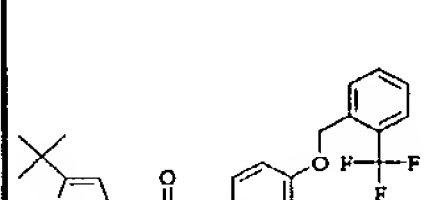

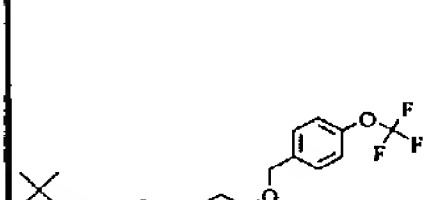
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	+++	ND
	+++	ND
	++	ND
	++	ND
	+++	++++

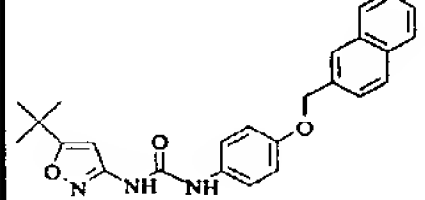
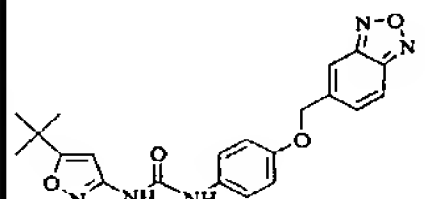
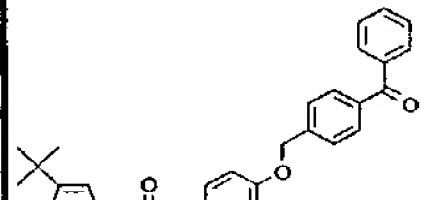
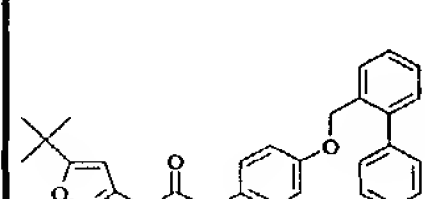
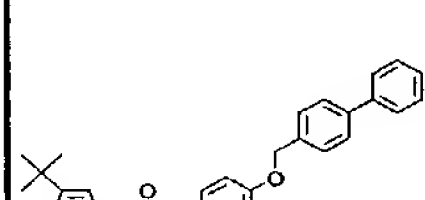

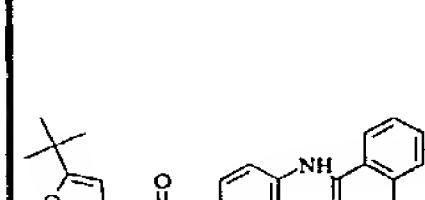
Compound Structure	Binding Assay:KIT (DKIN)
	+++
	++
	++
	++
	+++
	+++
	++++

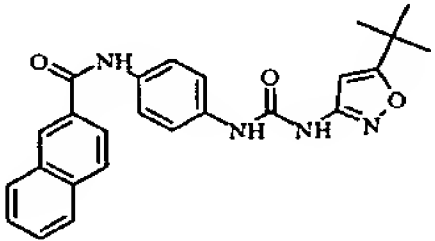
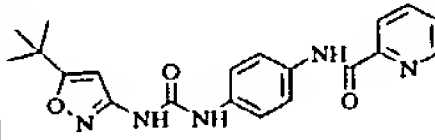
Compound Structure	Binding Assay:KIT (DKIN)
	+++
	+++
	++++
	++++

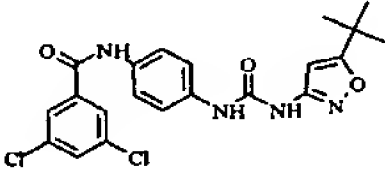
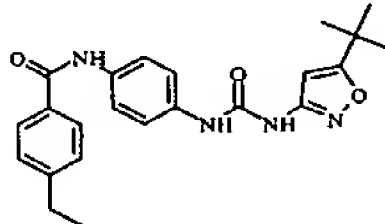
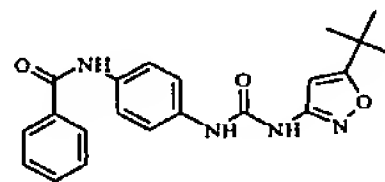
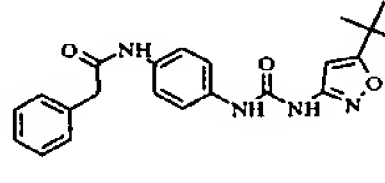
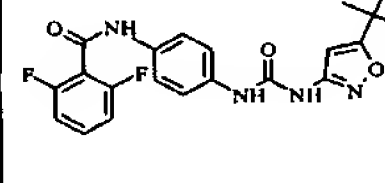
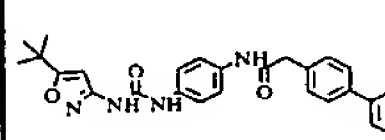
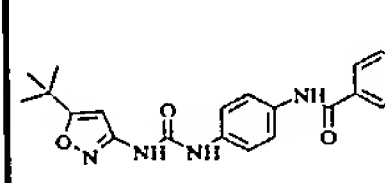
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)
	+++	++++	ND	++

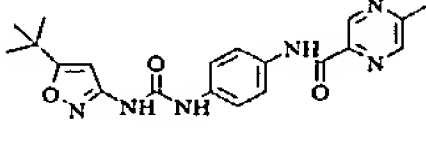
Compound Structure	Binding Assay:KIT (DKIN)
	+++
	+++
	+++
	++++
	+++
	++++
	+++

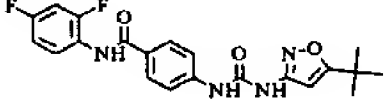
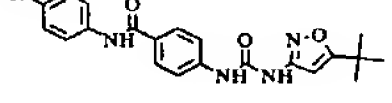

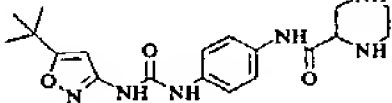
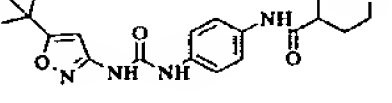
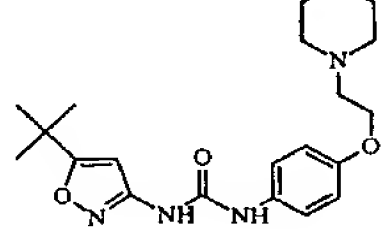
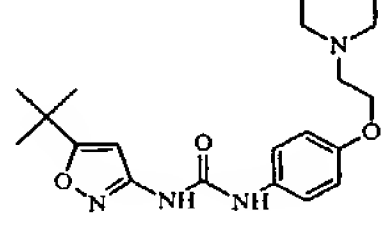
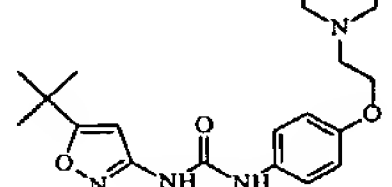
Compound Structure	Binding Assay:KIT (DKIN)
	+++
	++
	+++
	+++
	+++
	+++
	+++

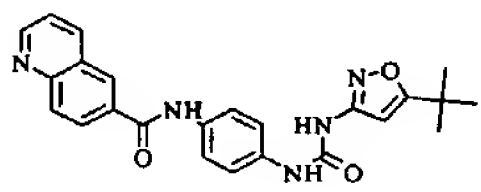
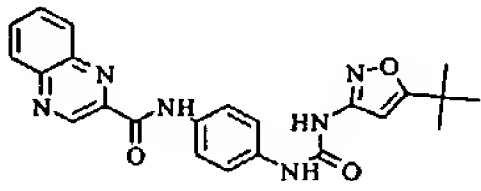
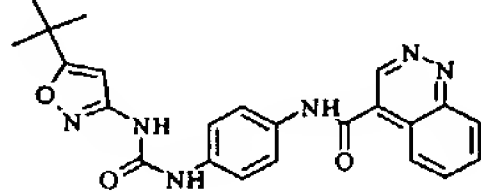
Compound Structure	Binding Assay:KIT (DKIN)
	+++
	+++
	+++
	++
	+++
	++++
	++++

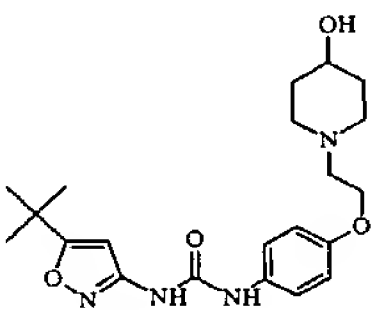
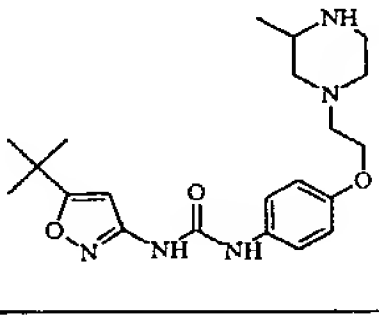
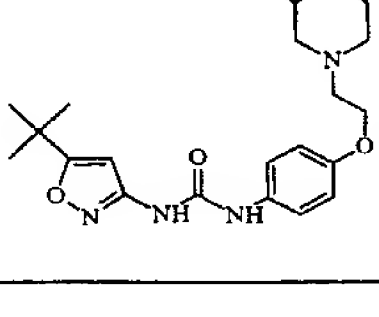
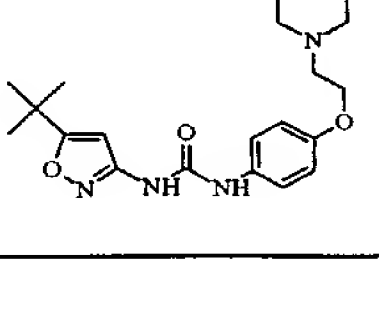
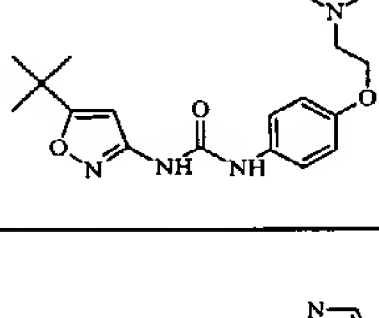
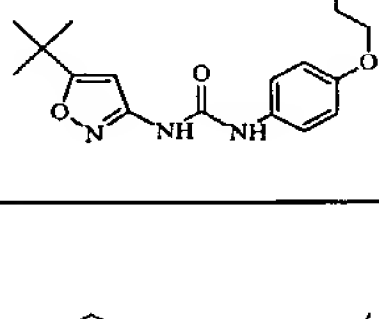
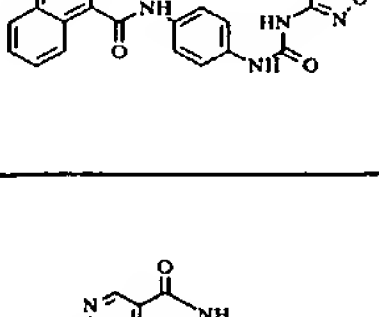
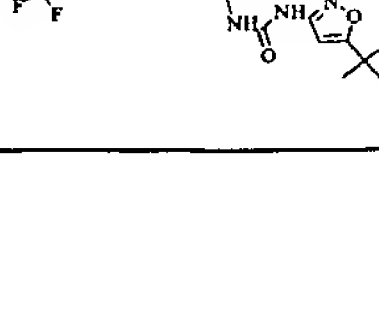
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)	Binding Assay:FLT 3(JMplus)
	++++	++++	ND	ND	ND
	++++	++++	ND	+++	+++

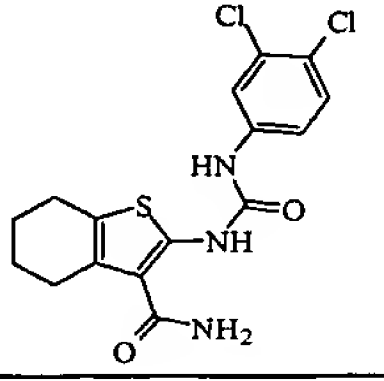
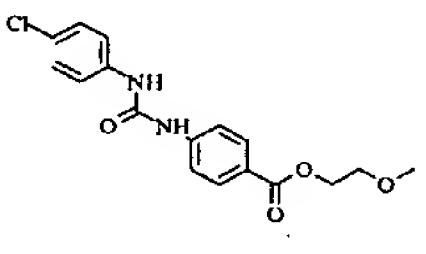
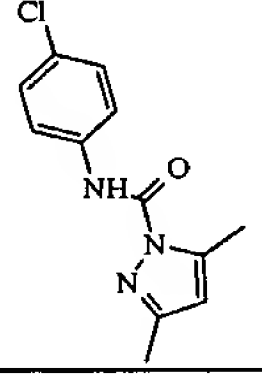
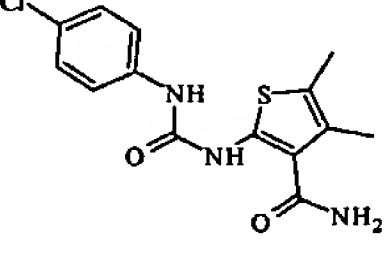
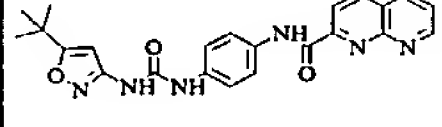
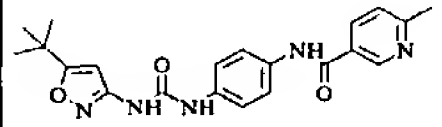
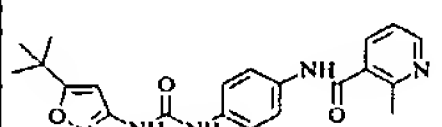
Compound Structure	Binding Assay:KIT (DKIN)
	+++
	+++
	+++
	+++
	++
	+++
	+++

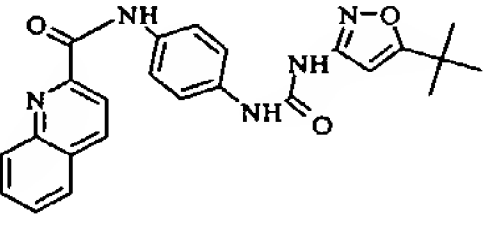
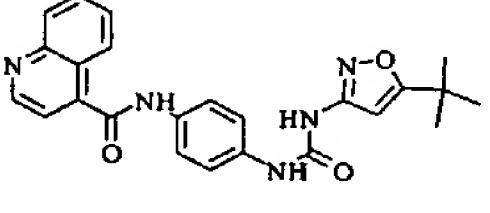
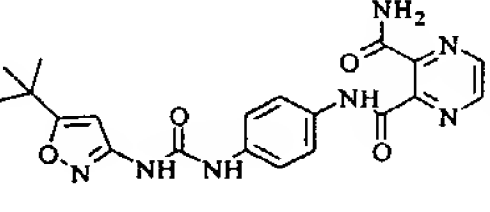
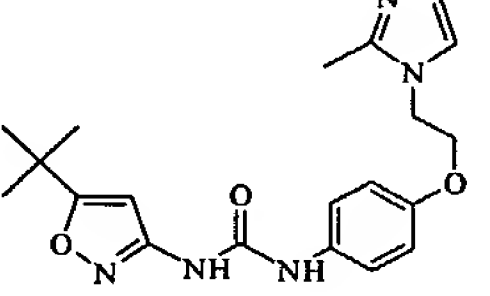
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)
	+++++	+++++	+++

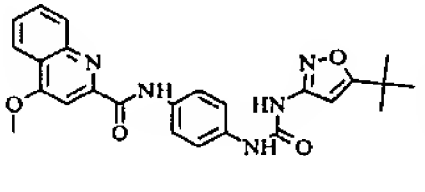
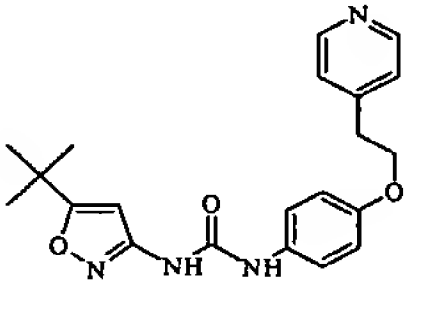
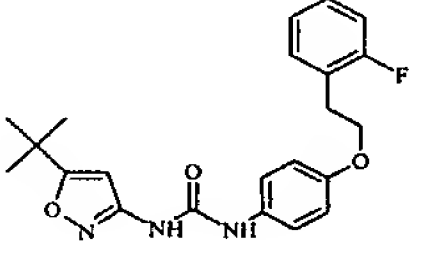
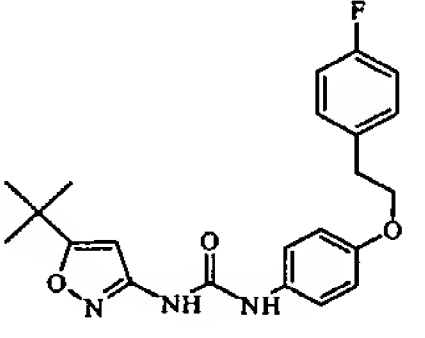
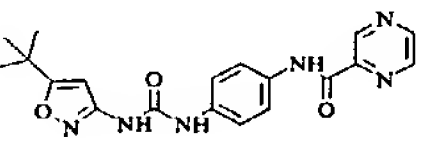
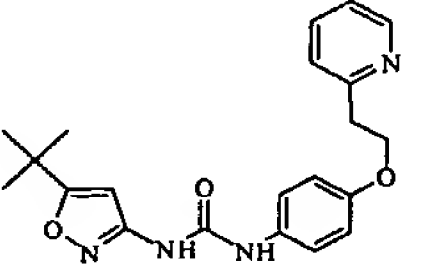
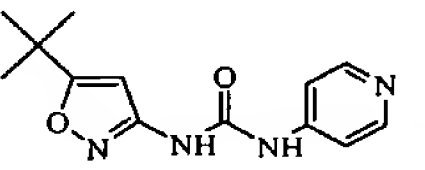
Compound Structure	Binding Assay:KIT (DKIN)
	+++
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	+
	+

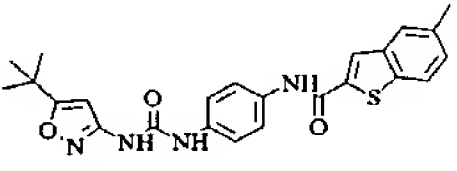
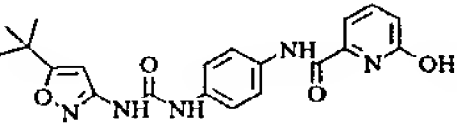
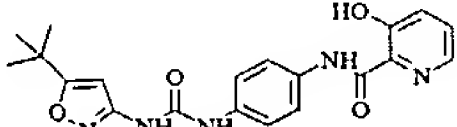
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)
	+++	ND	++
	++	ND	ND
	+++	ND	++++

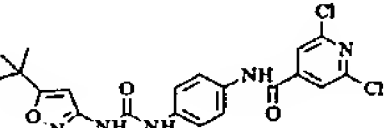
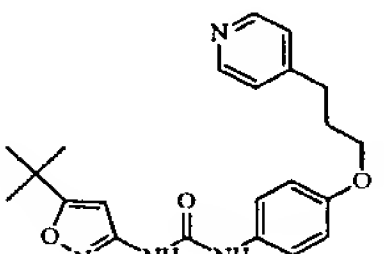
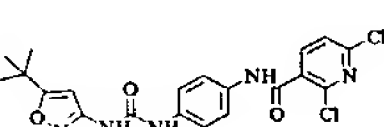
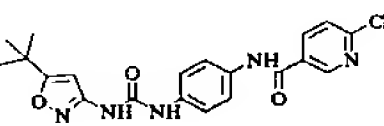
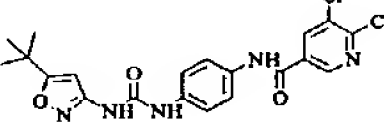
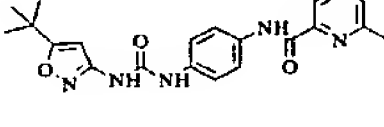
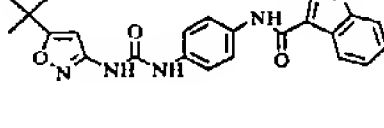
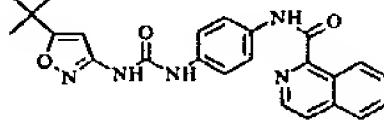
Compound Structure	Binding Assay:KIT (DKIN)
	+
	+
	+
	++
	++
	+++
	++
	++

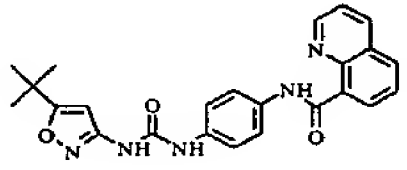
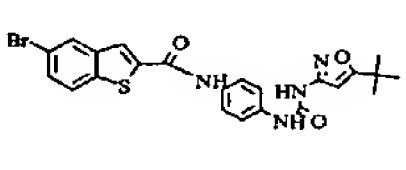
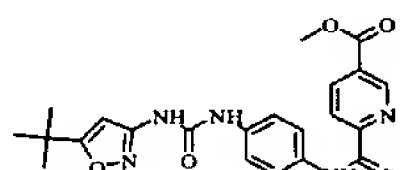
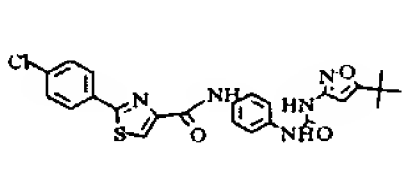
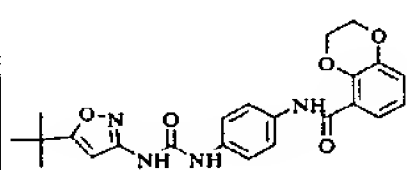
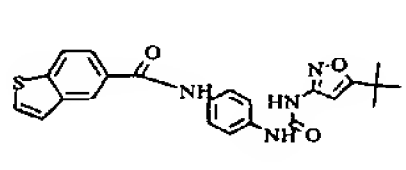
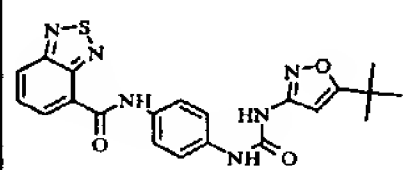
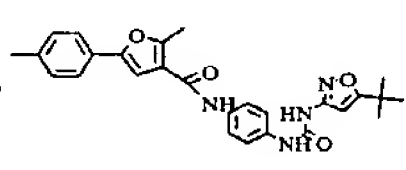
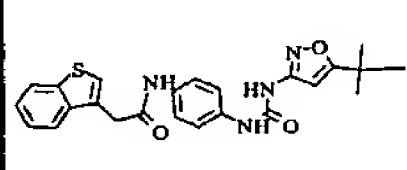
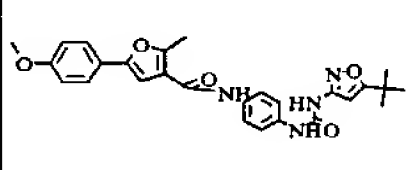

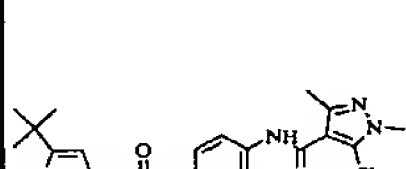
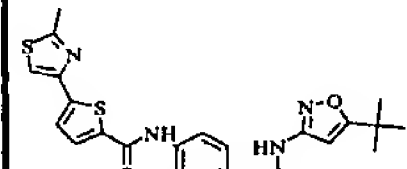
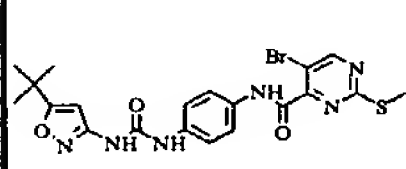
Compound Structure	Binding Assay:KIT (DKIN)
	+
	++
	+
	+++
	+++
	+++
	+++

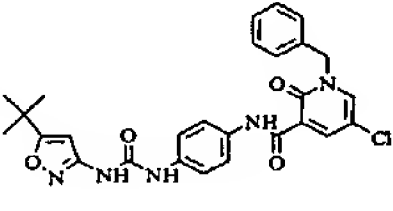
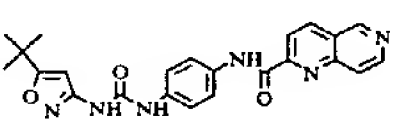
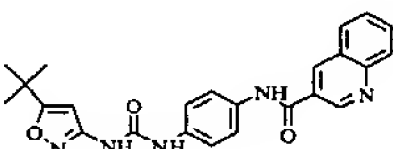
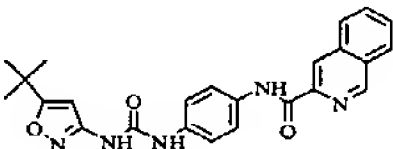
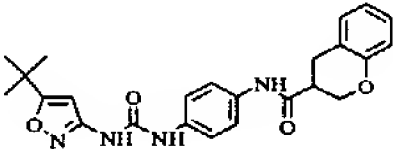
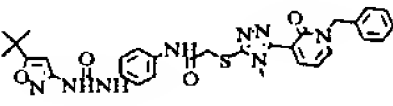
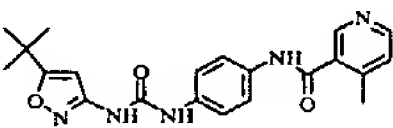
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	+++++	+++++
	+++	ND
	+++	ND
	+++	ND

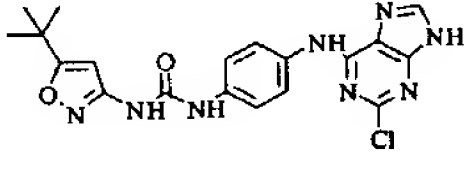
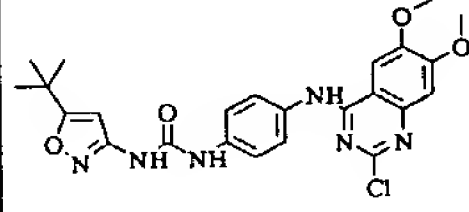
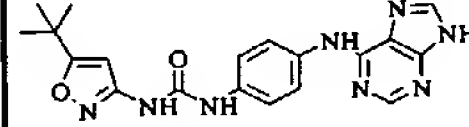
Compound Structure	Binding Assay:KIT (DKIN)
	+++
	++++
	+++
	+++
	++++
	+++
	++

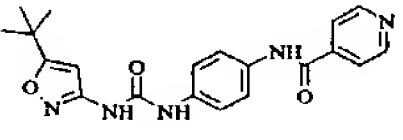
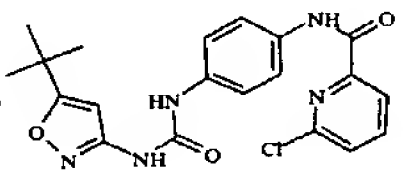
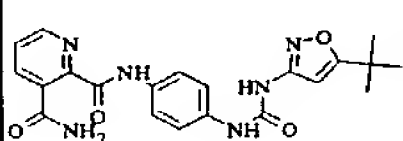
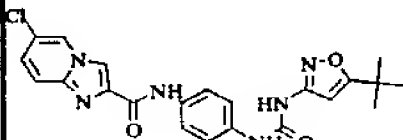
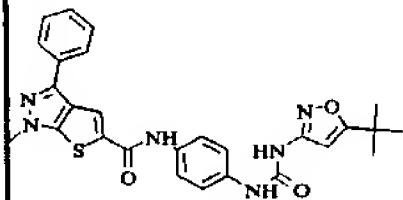
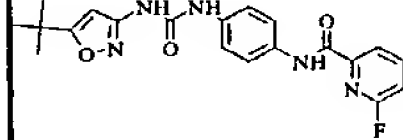
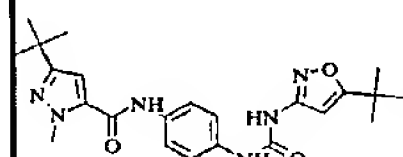
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)	Binding Assay:FLT 3(JMplus)
	++++	++++	ND	ND	ND
	++++	ND	ND	ND	ND
	++++	++++	++++	+++	+++

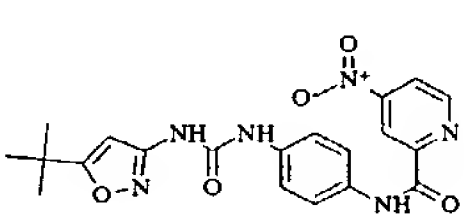
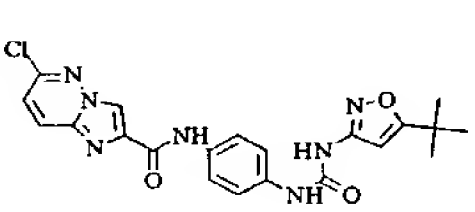
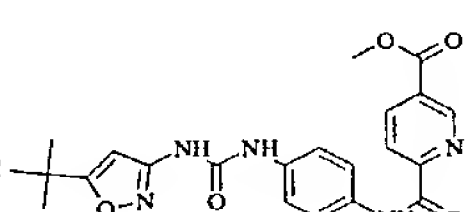
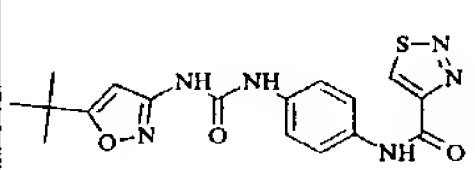
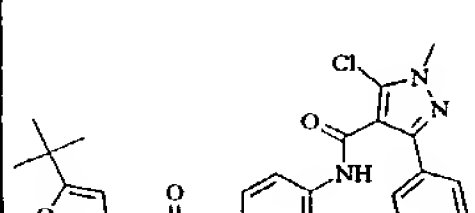
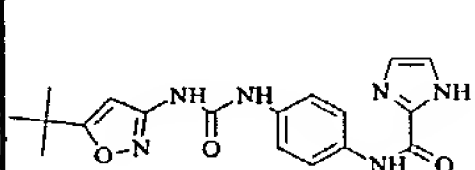
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	++	ND
	++++	++++
	++	ND
	++	ND
	++	ND
	++++	++++
	+++	ND
	ND	++++

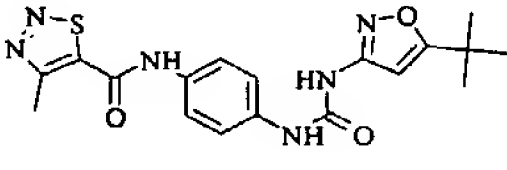
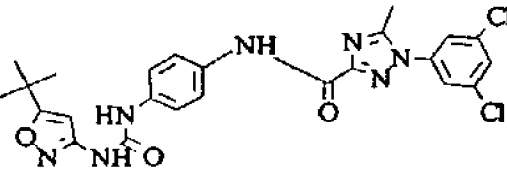
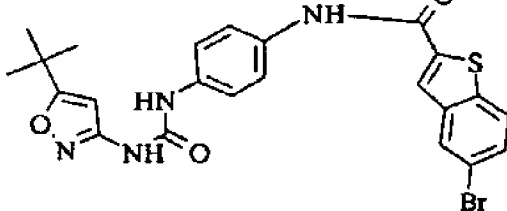
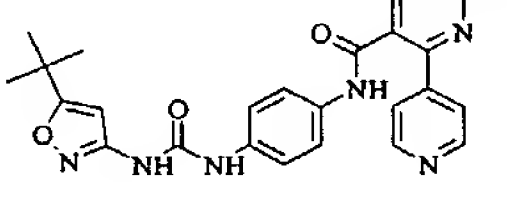
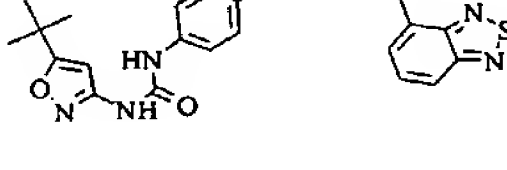
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	++++	ND		++	ND
	++++	ND		+++	ND
	++	ND		+++	++++
	+++	ND		++	ND
	++	ND		++	ND
	+++	ND		+++	ND
	+++	++++		+++	ND

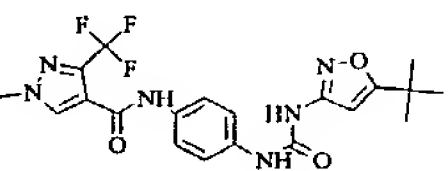
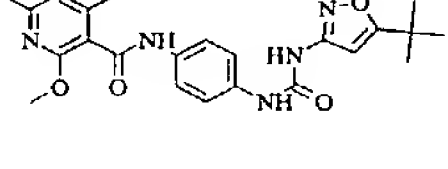
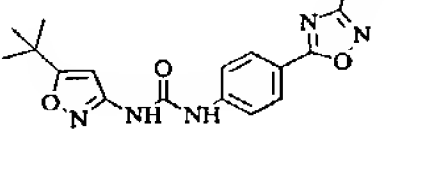
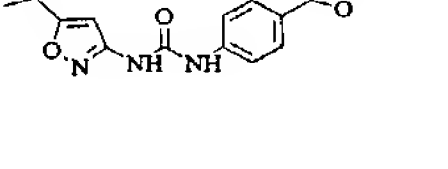
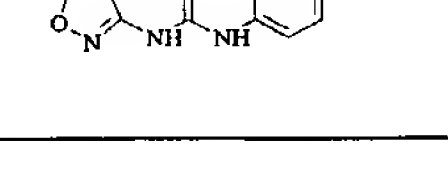

Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)	Binding Assay:FLT 3(JMplus)
	++	ND	ND	ND	ND
	++++	++++	ND	ND	ND
	+++	ND	++	ND	ND
	++++	++++	ND	ND	+++
	++	ND	ND	ND	ND
	+++	ND	ND	ND	ND
	+++	ND	ND	ND	ND

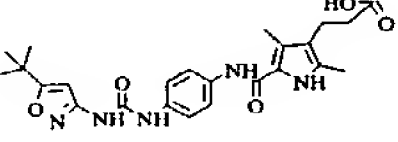
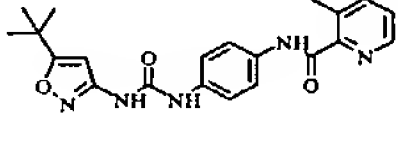
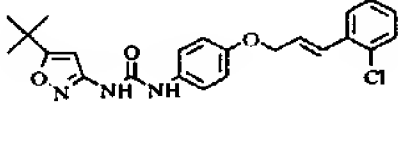
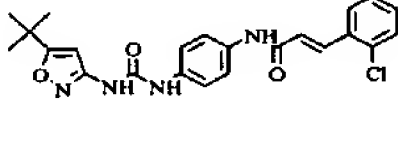
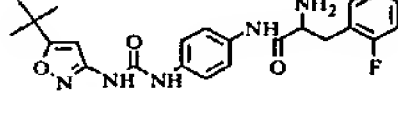
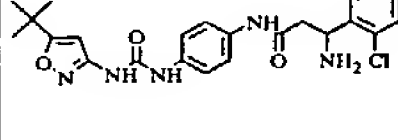
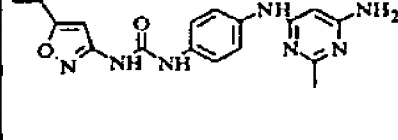
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)	Binding Assay:FLT 3(JMplus)	Binding Assay:KIT (JMplus, V 559D)
	++++	++++	++	ND	ND	ND
	+++	++++	++	++	ND	++++
	++++	ND	++++	++++	ND	ND

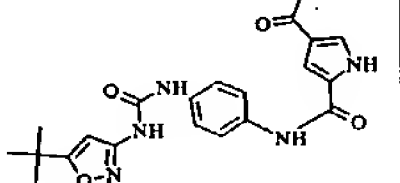
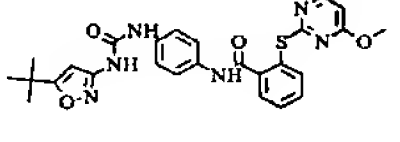
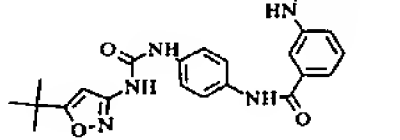
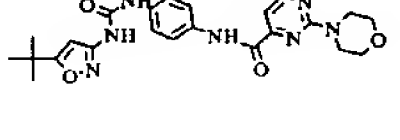
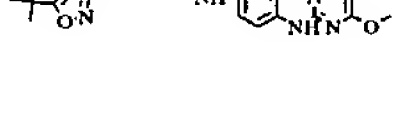
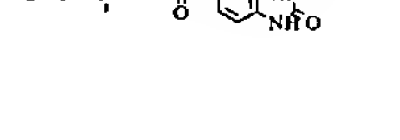
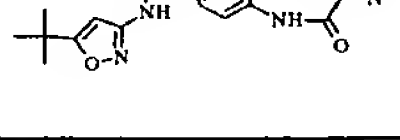
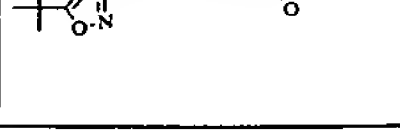
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	+++	ND
	++++	++++
	++	ND
	++++	ND
	+++	ND
	++++	++++
	+++	ND

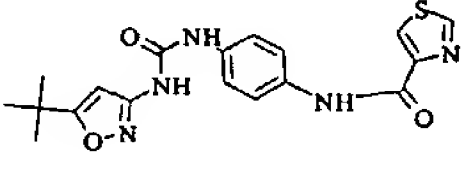
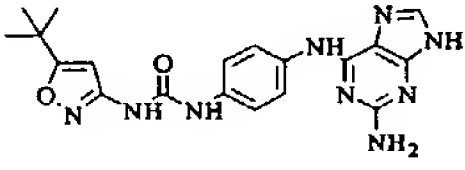
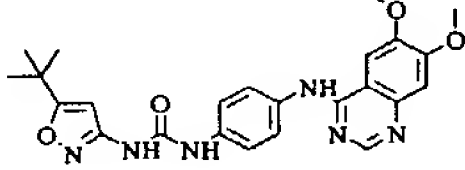
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	++++	ND
	++++	++++
	+++	ND
	+++	ND
	+	ND
	++++	ND

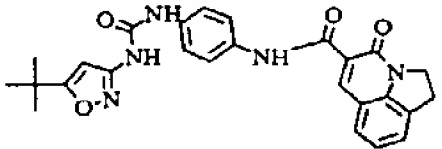
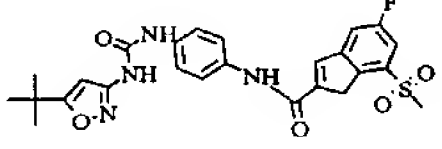
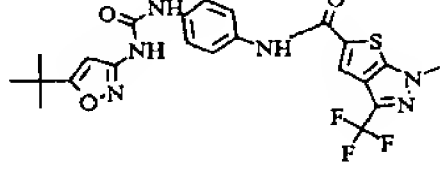
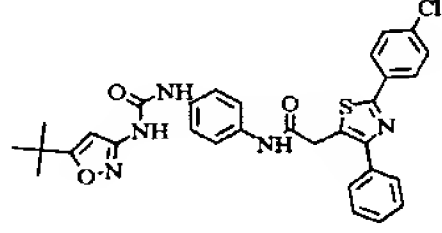
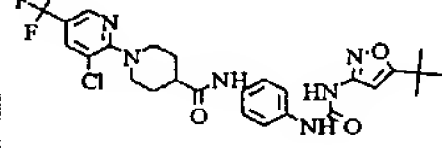
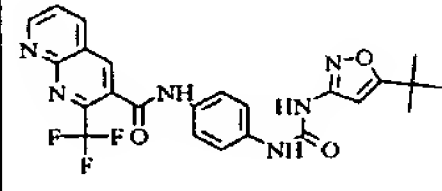
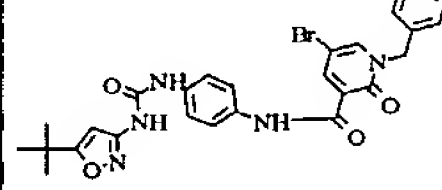
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)
	++	ND	ND
	+	ND	ND
	+++	ND	ND
	++	ND	ND
	++++	ND	++

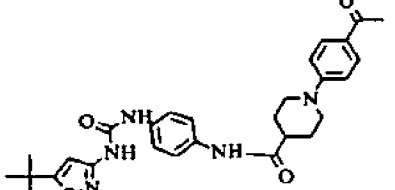
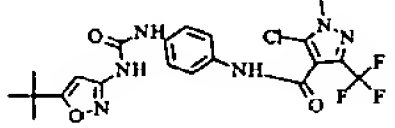
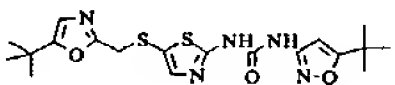
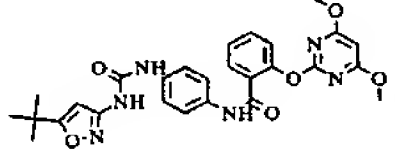
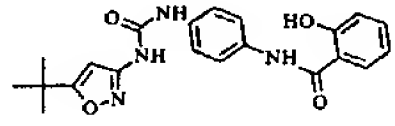
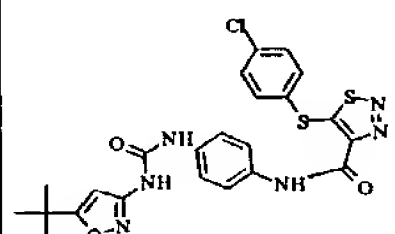
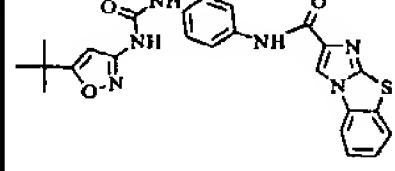
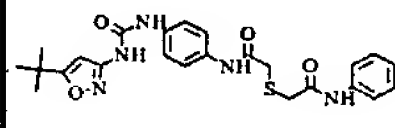
Compound Structure	Binding Assay:KIT (DKIN)
	+++
	++
	++
	++
	+++
	+++

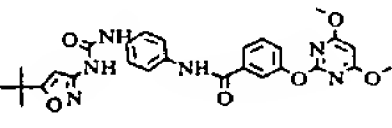
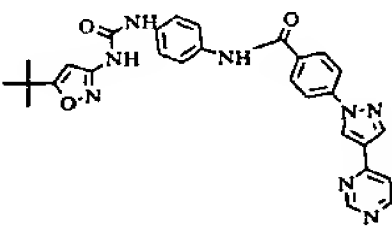
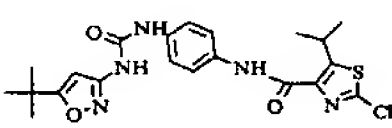
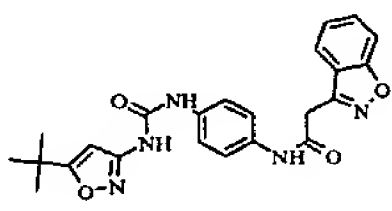
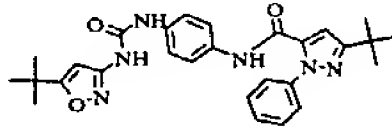
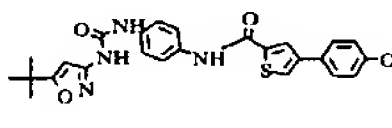

Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)
	++++	ND	ND	+++
	++++	++++	ND	ND
	+++	ND	ND	ND
	+++	++++	ND	ND
	++	ND	ND	ND
	++	ND	ND	ND
	+++	++++	ND	ND

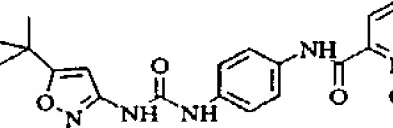
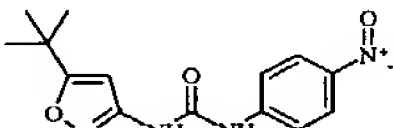
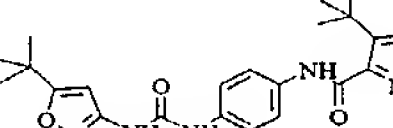
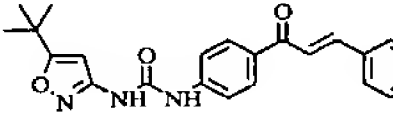
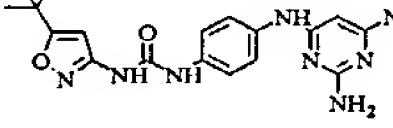
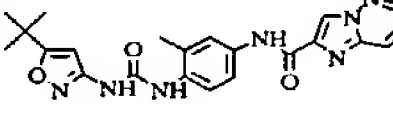
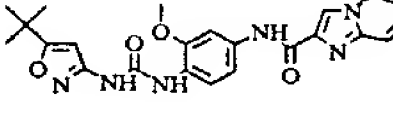
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	ND	++++
	ND	++++
	ND	++++
	ND	++++
	ND	++++
	ND	++++
	ND	+++
	ND	+++

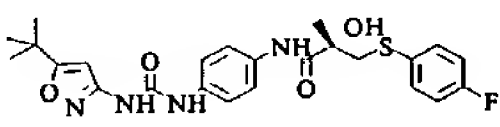
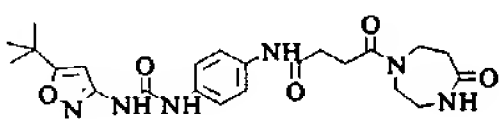
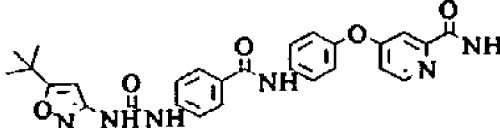
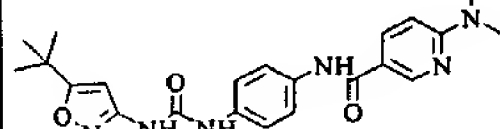
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)	Binding Assay:FLT 3(JMplus)	Binding Assay:KIT (JMplus, V 559D)
	ND	++++	+++	ND	ND	ND
	ND	++++	++++	ND	ND	ND
	ND	++++	++++	++++	ND	++++

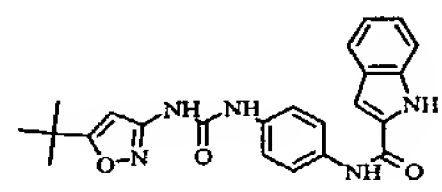
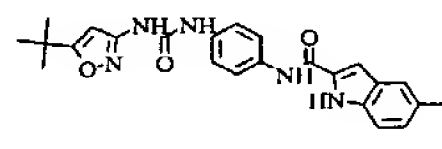
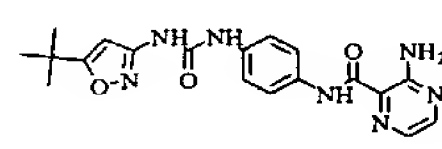
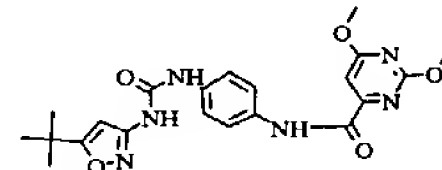
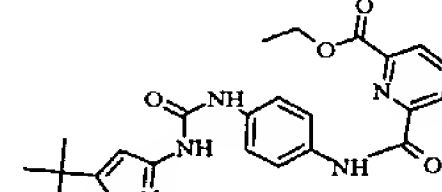
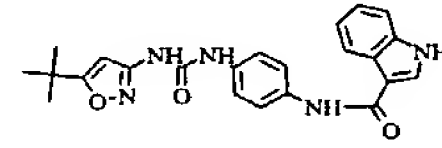
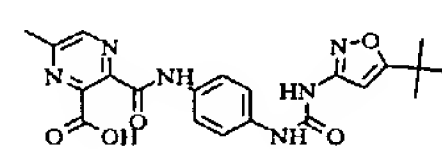
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	ND	++++
	ND	++++
	ND	+++
	ND	++++
	ND	+++
	ND	+++
	ND	++++

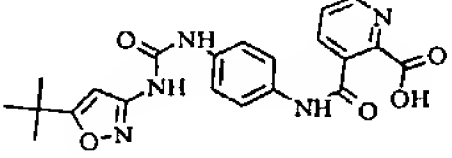
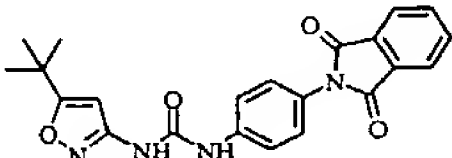
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	ND	++++
	ND	++++
	ND	+++
	ND	+++
	ND	++
	ND	+++
	ND	++++
	ND	++++

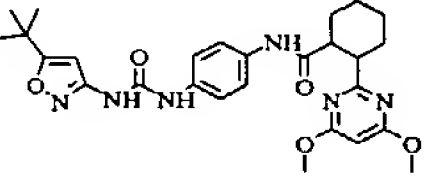
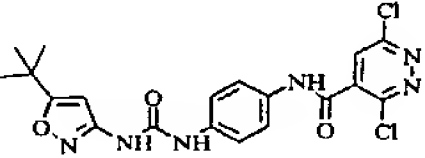
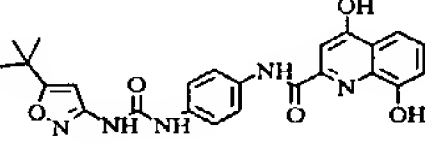
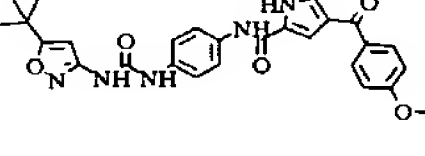
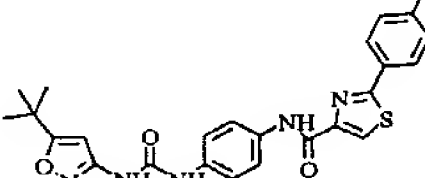
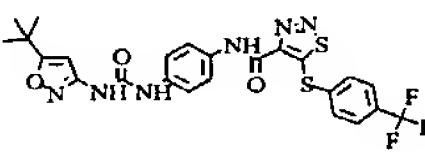
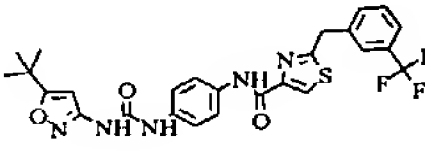
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)
	ND	++++	+++	+++
	ND	++++	ND	ND
	ND	++++	ND	ND
	ND	++++	ND	ND
	ND	++++	ND	ND
	ND	++++	ND	ND
	ND	++++	ND	+++

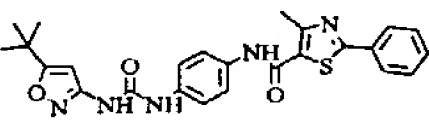

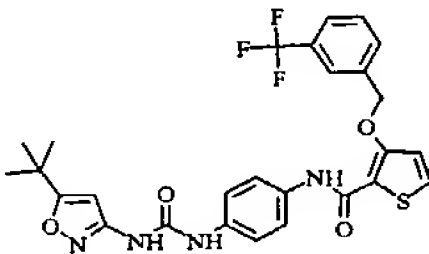

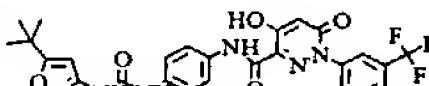
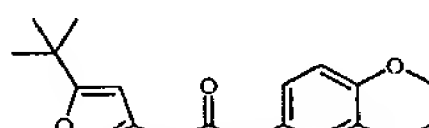
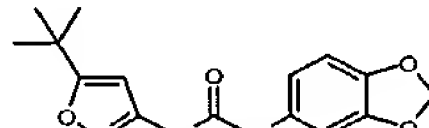
Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	ND	++++
	ND	++++
	ND	++++
	ND	++++
	ND	++++
	ND	++++
	ND	++++

Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	ND	++++
	ND	+++
	ND	++++
	ND	++++

Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)
	ND	++++	ND	++
	ND	++++	ND	++
	ND	++++	+++	++
	ND	++++	ND	ND
	ND	++++	ND	ND
	ND	++++	ND	ND
	ND	++++	++	ND

Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)	Binding Assay:MK NK2(DKIN)	Binding Assay:KIT (JMminus, D816V)
	ND	++++	ND	ND
	ND	++++	ND	++

Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	ND	+++
	ND	++++
	ND	++
	ND	+++
	ND	++++
	ND	++++
	ND	++++

Compound Structure	Binding Assay:KIT (DKIN)	Binding Assay:KIT (JMminus)
	ND	++++
	ND	+++
	ND	++++
	ND	++++
	ND	++++
	ND	++
	ND	+++

All references cited herein, including patents, patent applications, and publications, are

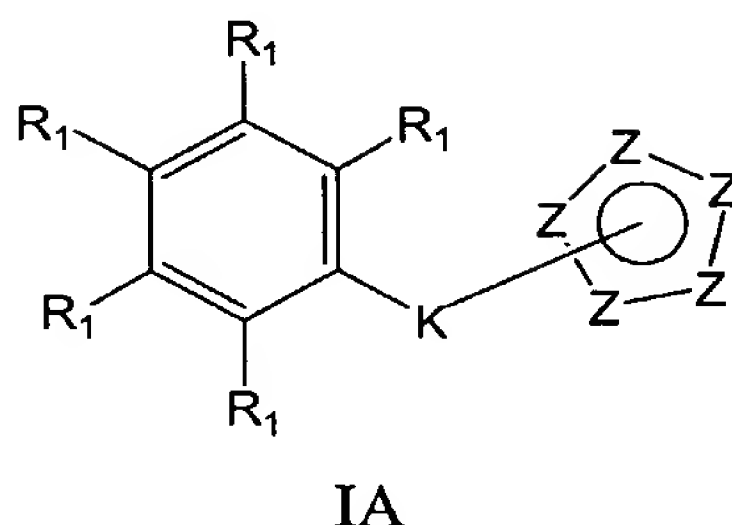
herby incorporated by reference in their entireties, whether previously specifically incorporated or not.

Having now fully described this invention, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters, concentrations, and conditions without departing from the spirit and scope of the invention and without undue experimentation.

While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth.

WHAT IS CLAIMED IS:

1. A compound corresponding to Formula (IA):



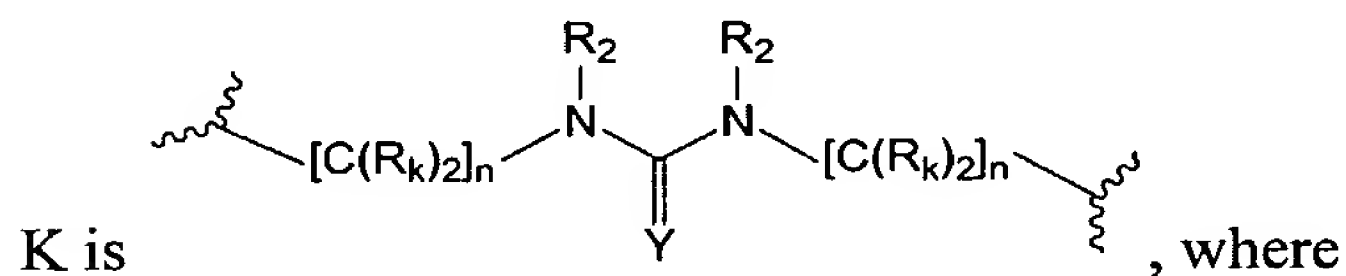
wherein:

each Z is independently C, CR₃, N, NR₃, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

where R₃ is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

each R₁ is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR_c, -OC(O)R_c, -NO₂, -N(R_c)₂, -SR_c, S(O)_jR_c where j is 1 or 2, -NR_cC(O)R_c, -C(O)N(R_c)₂, -C(O)₂R_c, or -C(O)R_c; or two adjacent R₁'s, are taken together to form a substituted or unsubstituted aryl or heteroaryl,

each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.



Y is O or S;

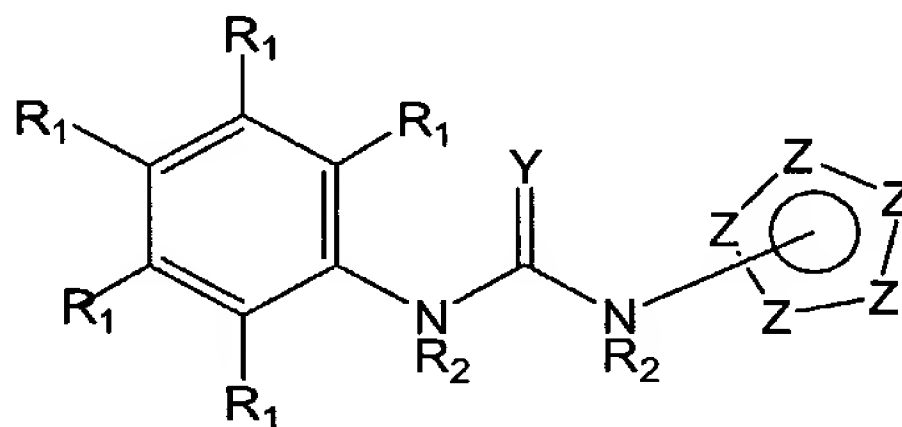
each R_k is independently H, halogen, substituted or unsubstituted alkyl, $-OR_d$, substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, $-C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$, or $-N(R_d)C(O)R_d$, where each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

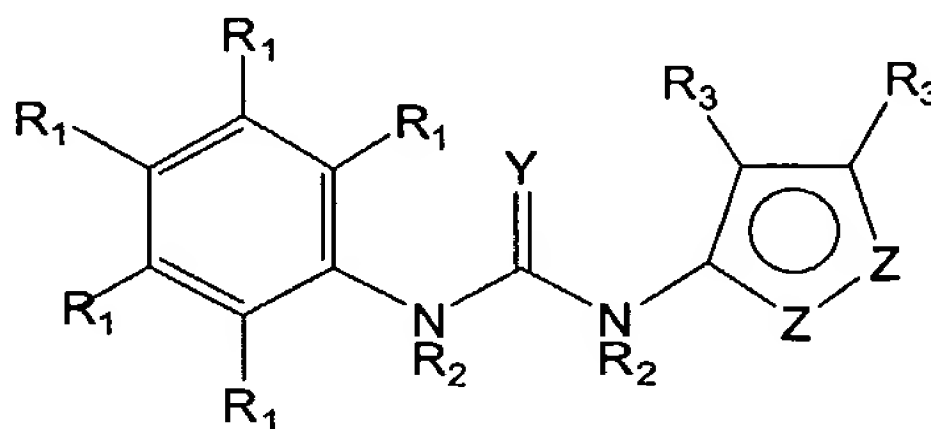
or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, corresponding to Formula (I):



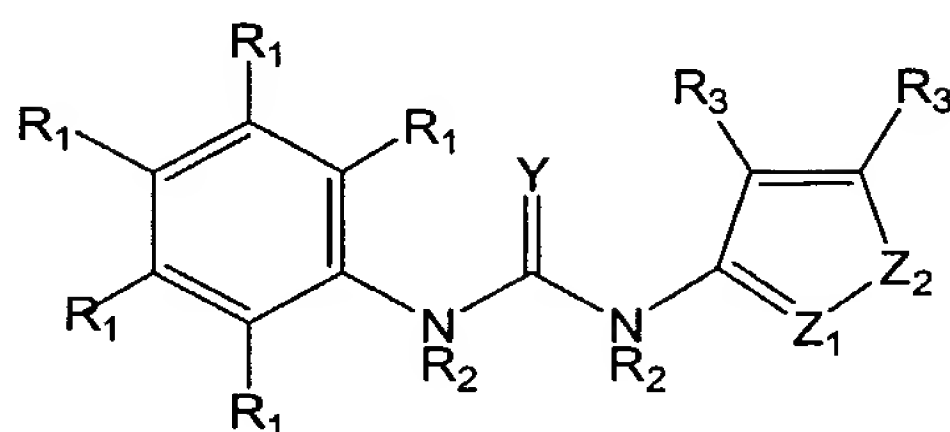
(I).

3. The compound of claim 1, corresponding to Formula (II):



(II).

4. The compound of claim 3, corresponding to Formula (III):



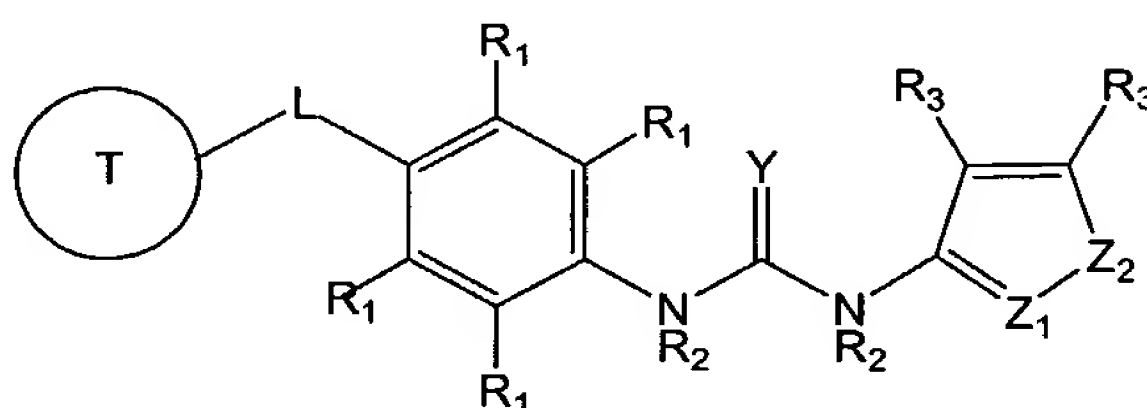
(III)

wherein:

Z_1 is CR_3 or N; and

Z_2 is O or S.

5. The compound of claim 4, corresponding to Formula (IV):



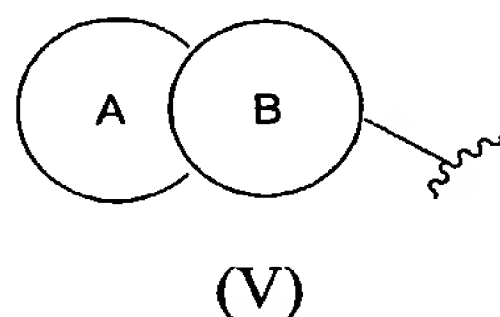
(IV)

wherein:

L is a linker selected from the group consisting of a covalent bond, -(substituted or unsubstituted alkylene)-, -(substituted or unsubstituted alkenylene)-, -O-, -O(substituted or unsubstituted alkylene)-, -C(O)-, -C(O)(substituted or unsubstituted alkylene)-, -C(O)(substituted or unsubstituted alkenylene)-, -NH-, -NH(substituted or unsubstituted alkylene)-, -NH(substituted or unsubstituted alkenylene)-, -C(O)NH-, -C(O)NH(substituted or unsubstituted alkylene)-, -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -S-, -S(substituted or unsubstituted alkylene)-, and -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-; and

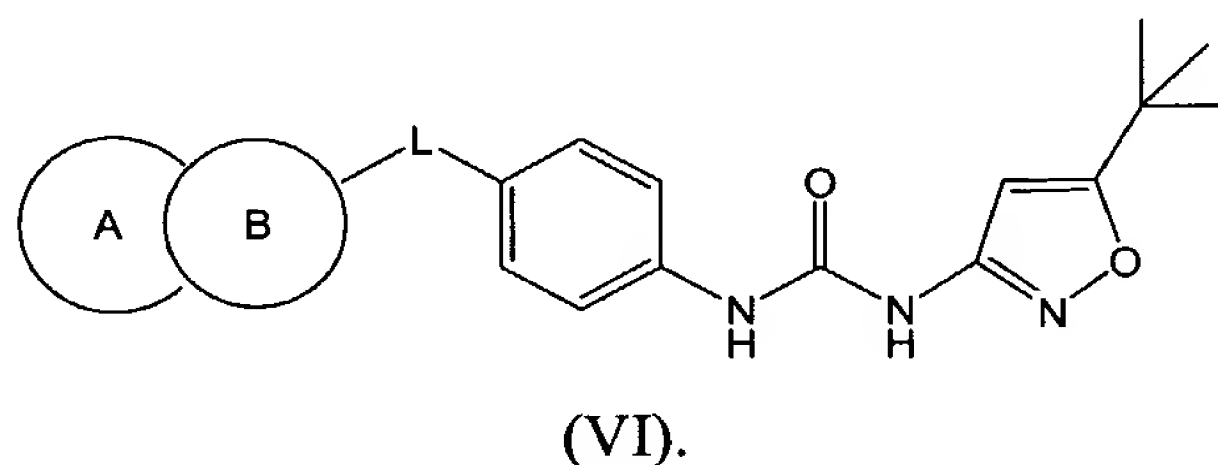
T is a mono-, bi-, or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

6. The compound of claim 5, wherein T corresponds to Formula (V):

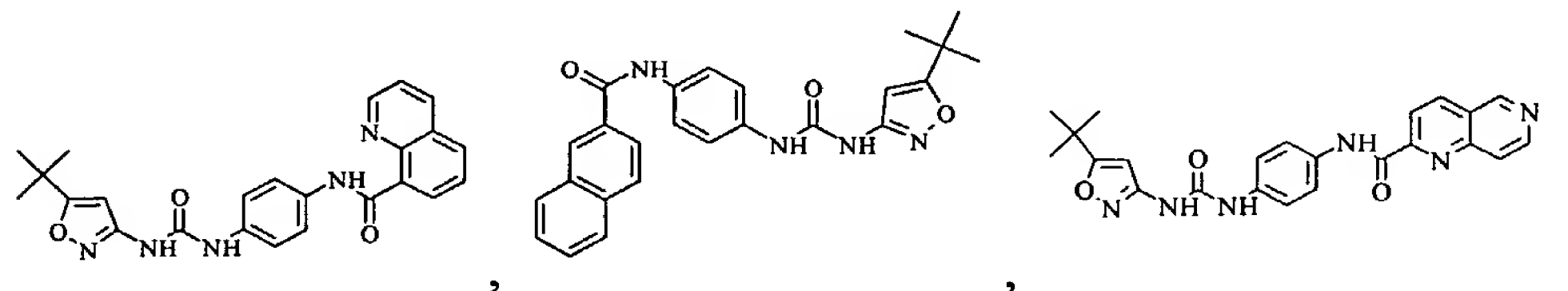


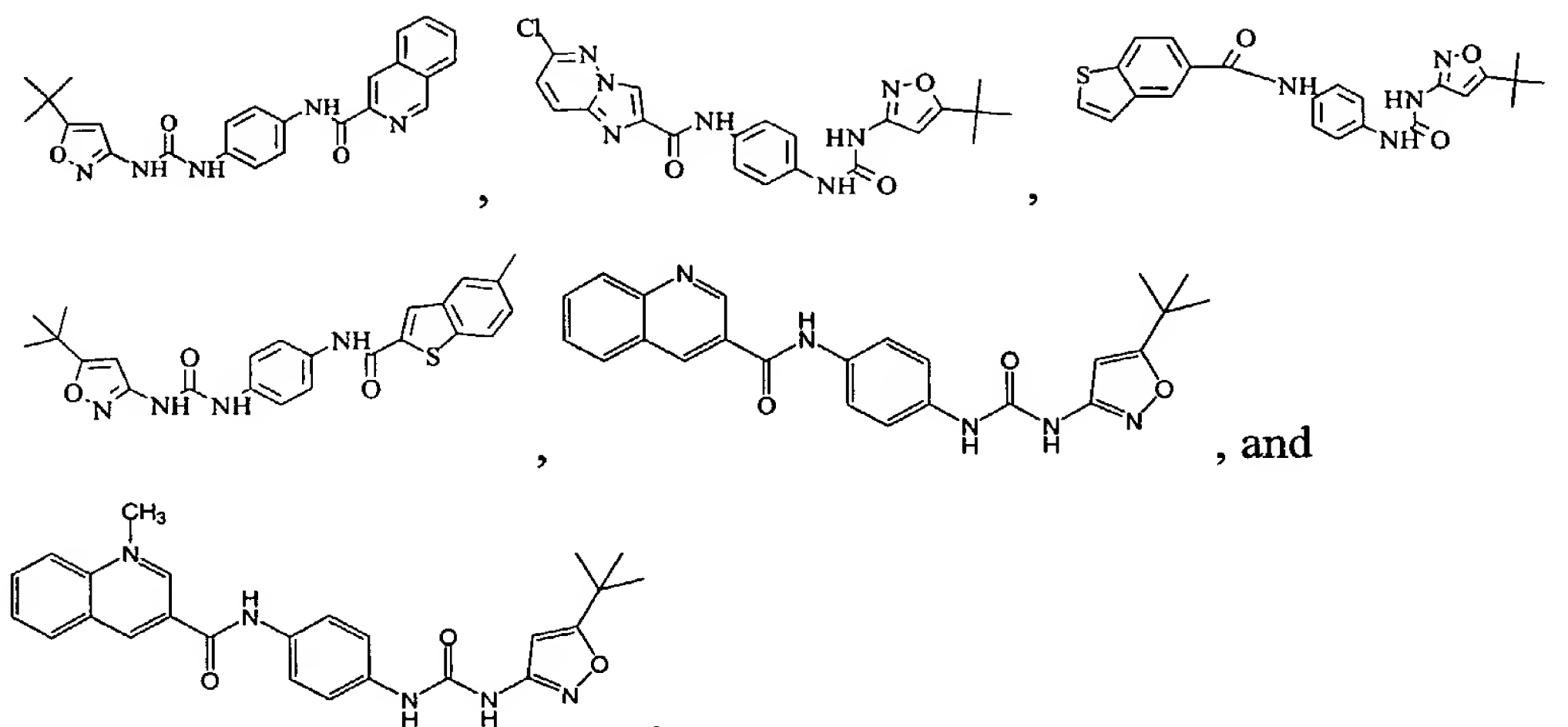
wherein A is a substituted or unsubstituted five or six-membered aryl, heterocyclyl or heteroaryl; and B is a substituted or unsubstituted five or six-membered arylene, heterocyclene or heteroarylene, wherein A and B together form a fused two-ring moiety.

7. The compound of claim 6, corresponding to Formula (VI):

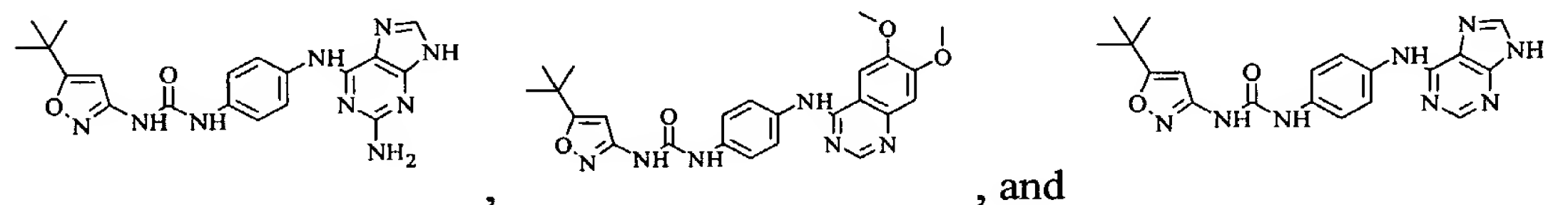


8. The compound of claim 7, wherein L is $-\text{C}(\text{O})\text{NH}-$.
9. The compound of claim 8, wherein B is substituted or unsubstituted phenylene, pyridinylene, pyrimidinylene, pyridazinylene, thiophenylene, imidazolylene, or pyrrolylene.
10. The compound of claim 9, selected from the group consisting of:

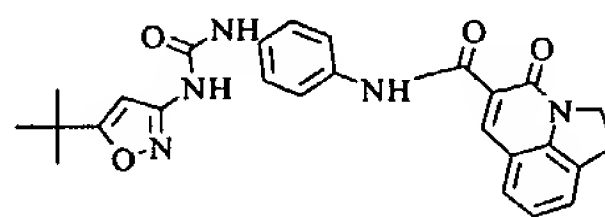




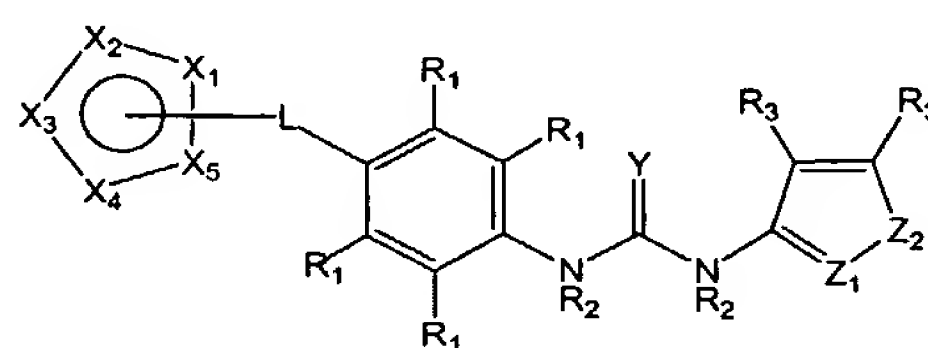
11. The compound of claim 7, wherein L is -NH- .
12. The compound of claim 11, wherein B is substituted or unsubstituted phenylene, pyridinylene, pyrimidinylene, pyridazinylene, thiophenylene, or imidazolylene.
13. The compound of claim 12, selected from the group consisting of:



14. The compound of claim 5, corresponding to:



15. The compound of claim 5, corresponding to Formula (VII):



(VII)

wherein:

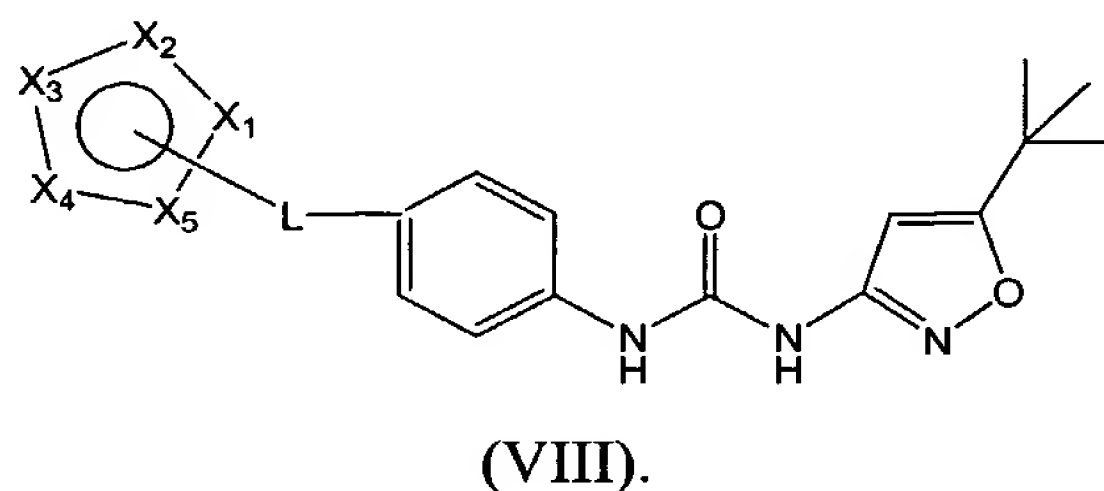
each of X_1 - X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1 - X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -S(O)_j R_d where j is 1 or 2,

-NR_d C(O) R_d , -C(O)₂ R_d , -C(O)N(R_d)₂, or -C(O) R_d , or two adjacent R_d s are taken together to form a substituted or unsubstituted aryl or hetroaryl,

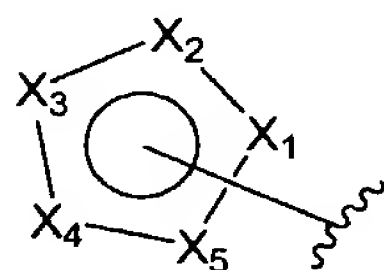
where each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

16. The compound of claim 15, corresponding to Formula (VIII):

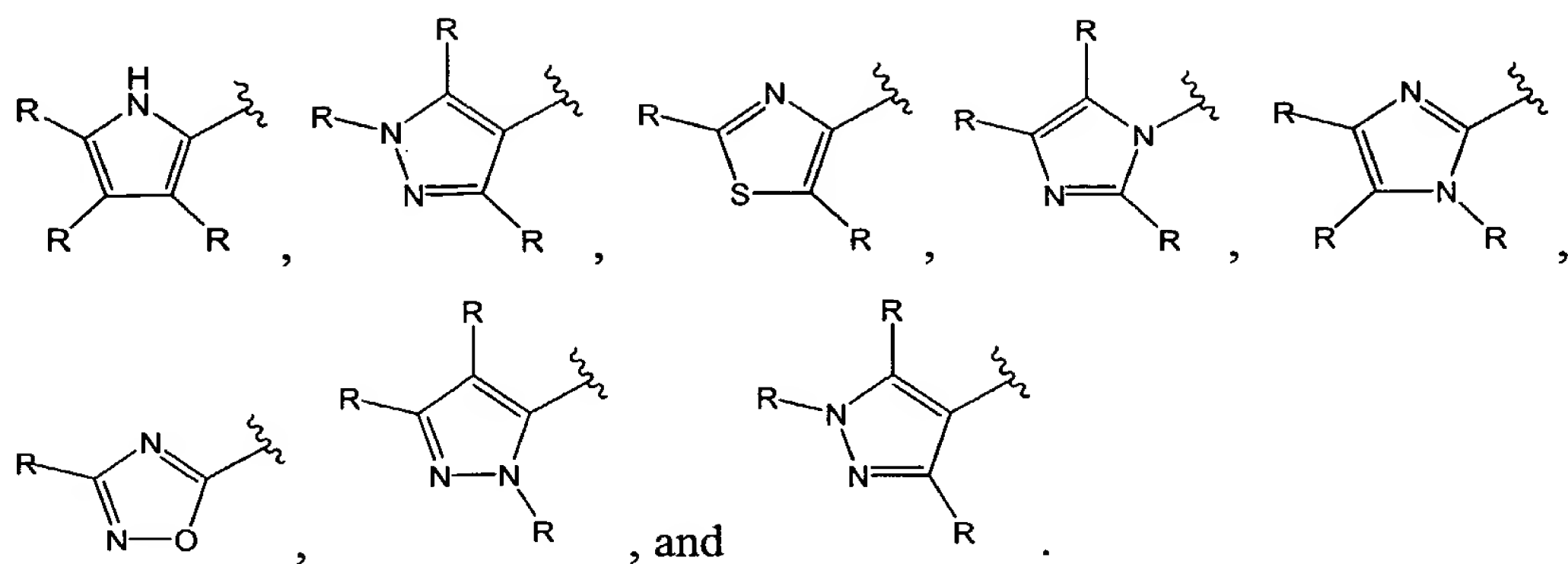


17. The compound of claim 16, wherein L is a covalent bond, -C(O)NH-, -OCH₂-, or -OCH₂CH₂-.

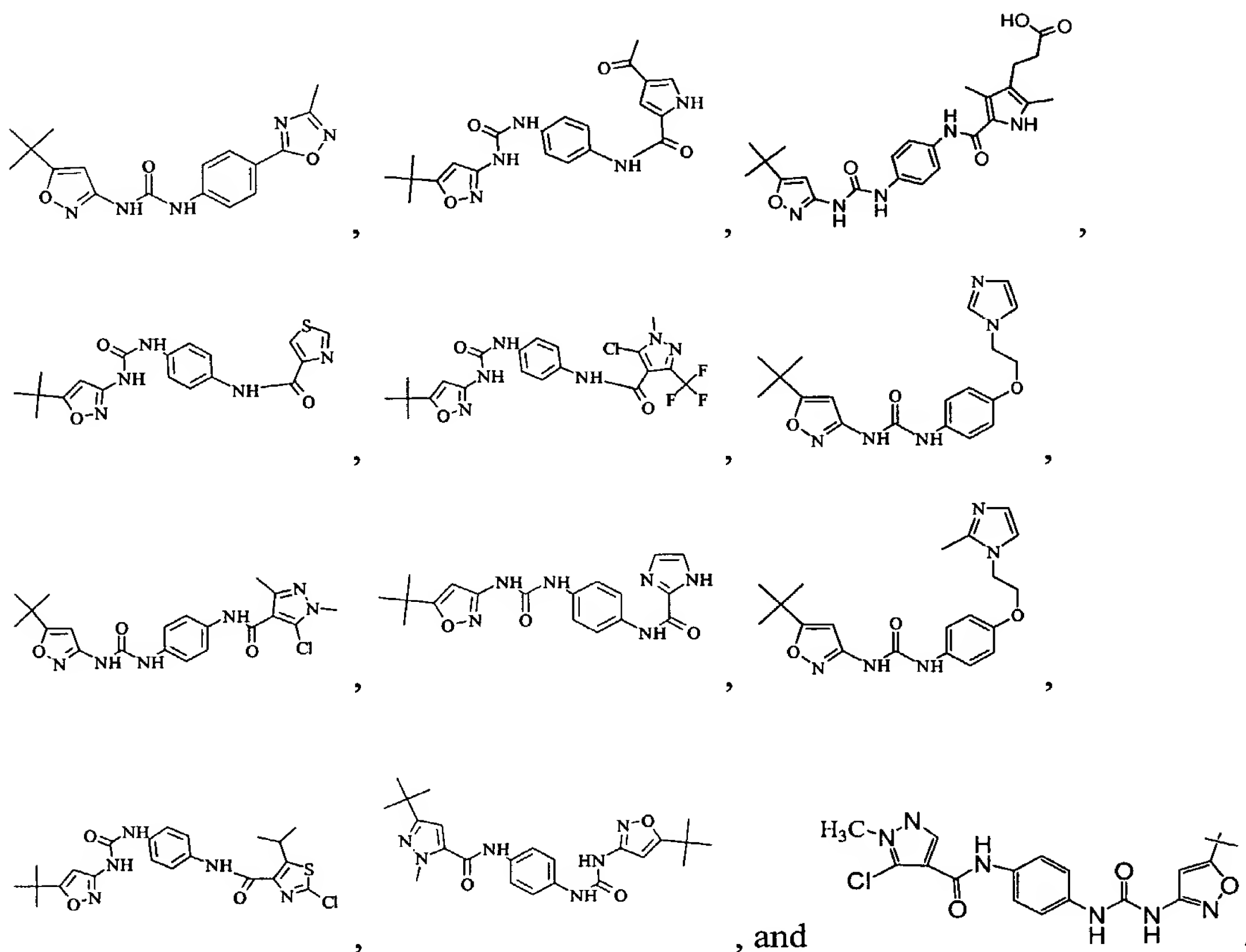
18. The compound of claim 16, wherein



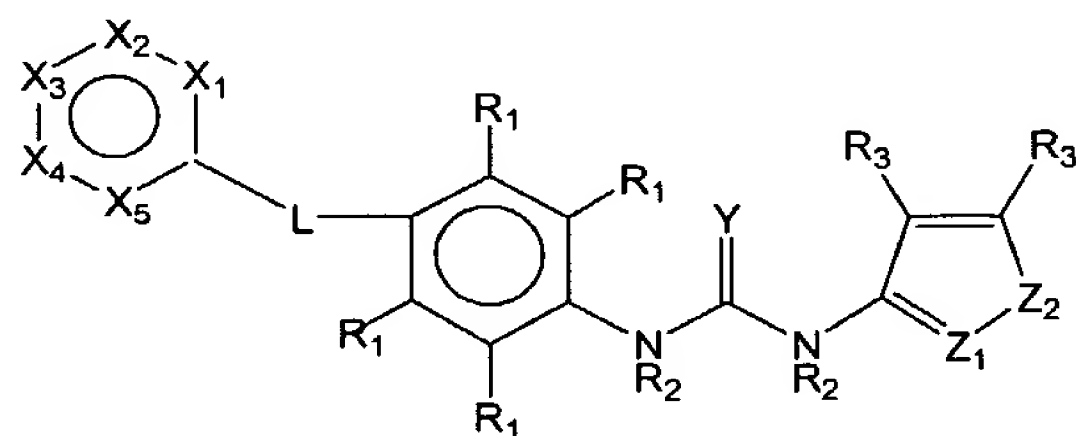
is selected from the group consisting of:



19. The compound of claim 18 selected from the group consisting of:

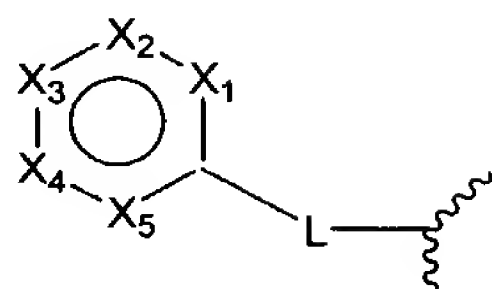


20. The compound of claim 5, corresponding to Formula (IX):



(IX)

wherein:



is selected from the group consisting of:

- (a) L is selected from the group consisting of -O(substituted or unsubstituted alkylene)-, and -C(O)(substituted or unsubstituted alkenylene)-; and

each of X_1 - X_5 is independently CR, N-O, or N, wherein no more than two of X_1 - X_5 is N, where

each R is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O) R_d , -NO₂, -N(R_d)₂, -SR_d, -NR_dC(O) R_d , or -C(O) R_d ,

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- (b) L is -NH-;

each of X_1 , X_2 , X_4 , and X_5 is independently CR, N-O, or N; and

X_3 is independently CR₅ or N, wherein no more than two of X_1 - X_5 is N, where

R_5 is selected from the group consisting of H, halogen, substituted or unsubstituted alkyl, substituted alkoxy, -C(O) R_d , -OC(O) R_d , -NO₂, -N(R_d)₂, and -SR_d, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- (c) L is -NH-;

each of X_1 , X_3 , and X_5 is independently CR, N-O, or N; and

each of X_2 and X_4 is independently CR_6 or N, wherein no more than two of X_1 - X_5 is N; where

R_6 is selected from the group consisting of H, halogen, unsubstituted alkyl,

-OH, substituted or unsubstituted alkoxy, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, $-SR_d$, and alkyl substituted with alkoxy, halogen, aryl, heteroaryl, amine, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, and $-SR_d$, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

(d) L is $-C(O)NH-$;

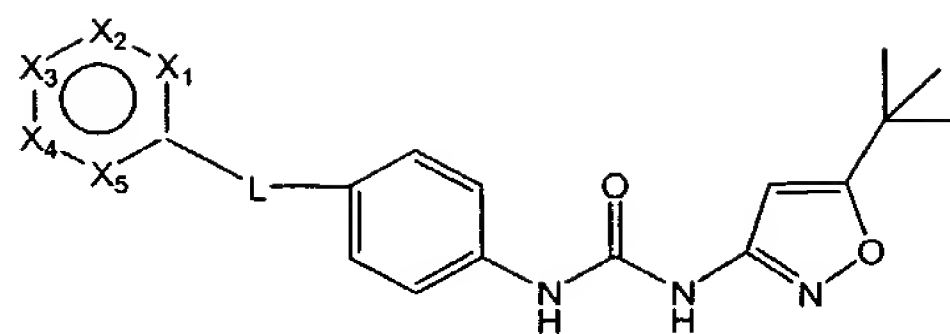
each of X_1 , X_2 , X_4 , and X_5 is independently CR, N-O, or N; and

X_3 is independently CR_7 or N, wherein no more than two of X_1 - X_5 is N, and when X_3 is N, at least one of X_1 , X_2 , X_3 , or X_5 is not CH, where

R_7 is selected from the group consisting of H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-C(O)R_d$, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$, and $-SR_d$, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

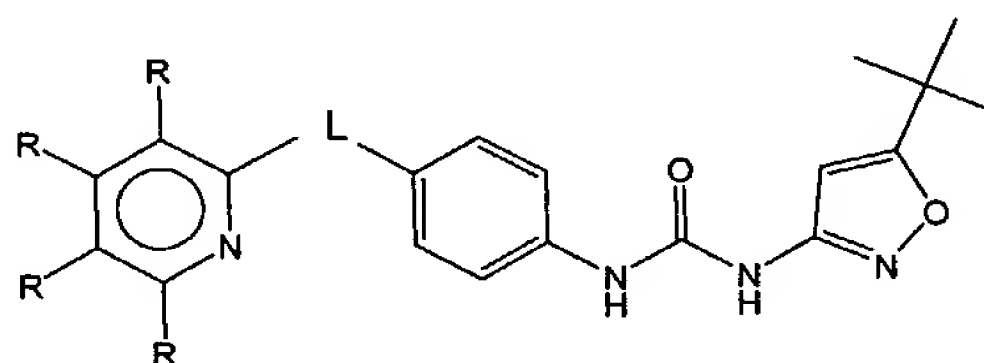
21. The compound of claim 20, corresponding to Formula (X):



(X).

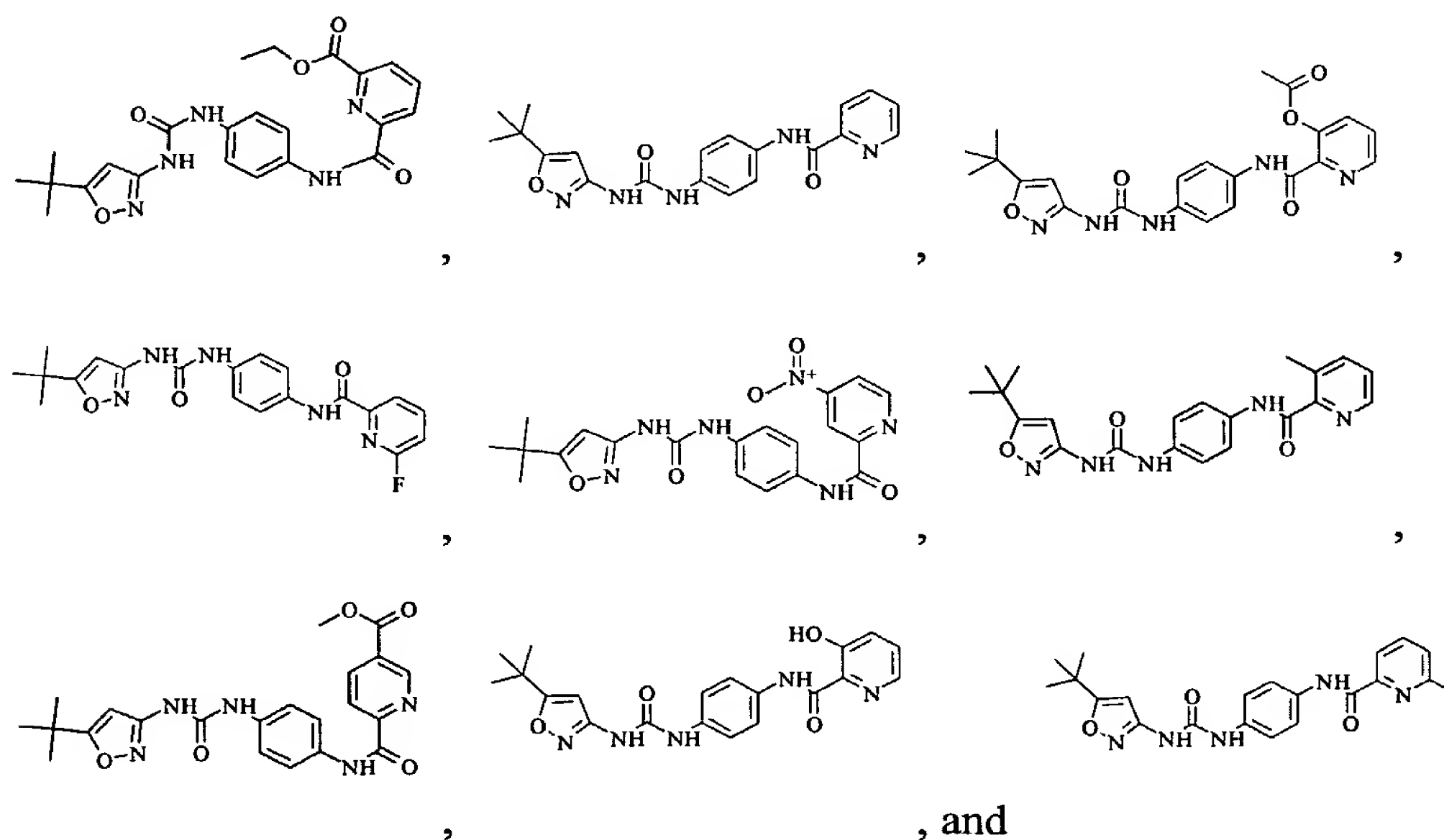
22. The compound of claim 21, wherein L is a linker selected from the group consisting of a covalent bond, -(substituted or unsubstituted alkylene), -NHC(O)-, -C(O)NH(substituted or unsubstituted alkylene), -NHC(O)(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene), -NHC(O)(substituted or unsubstituted alkenylene)-, and -O(substituted or unsubstituted alkylene)-.

23. The compound of claim 22, corresponding to Formula (XI):

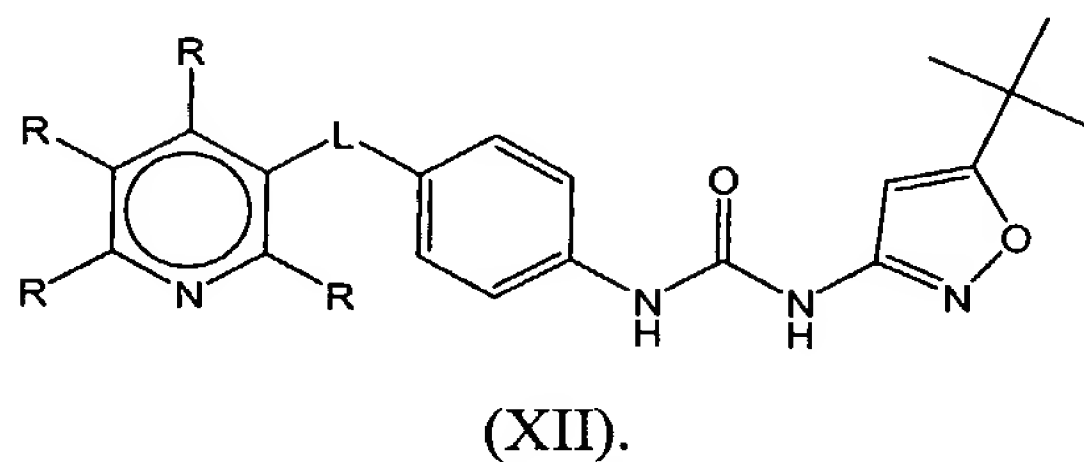


(XI).

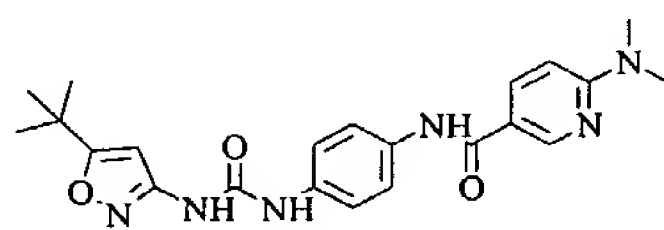
24. The compound of claim 23, selected from the group consisting of:



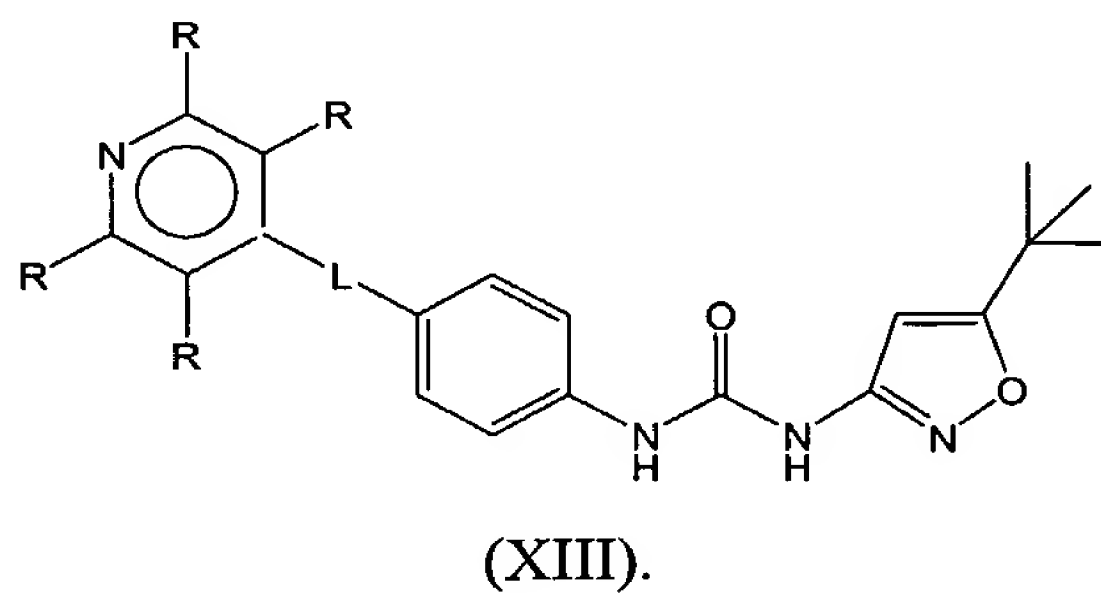
25. The compound of claim 21, corresponding to Formula (XII):



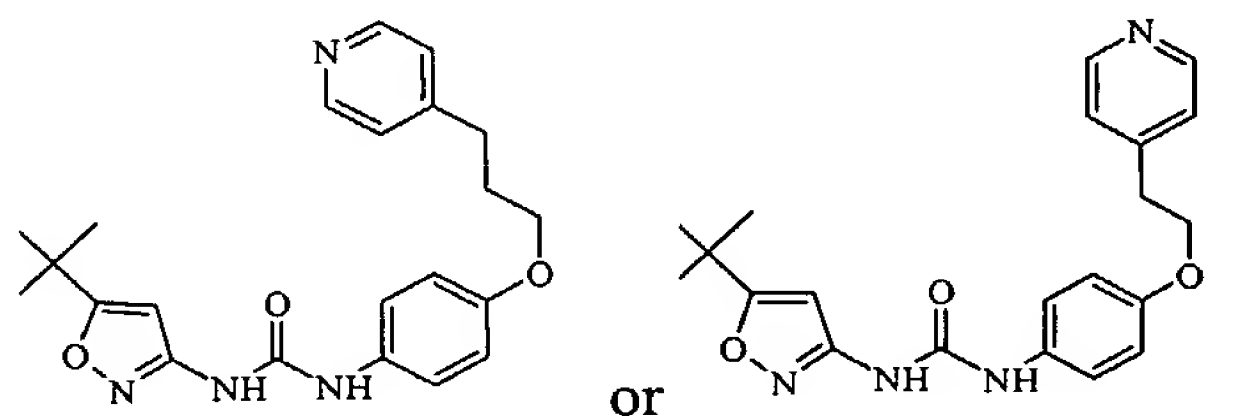
26. The compound of claim 25, corresponding to:



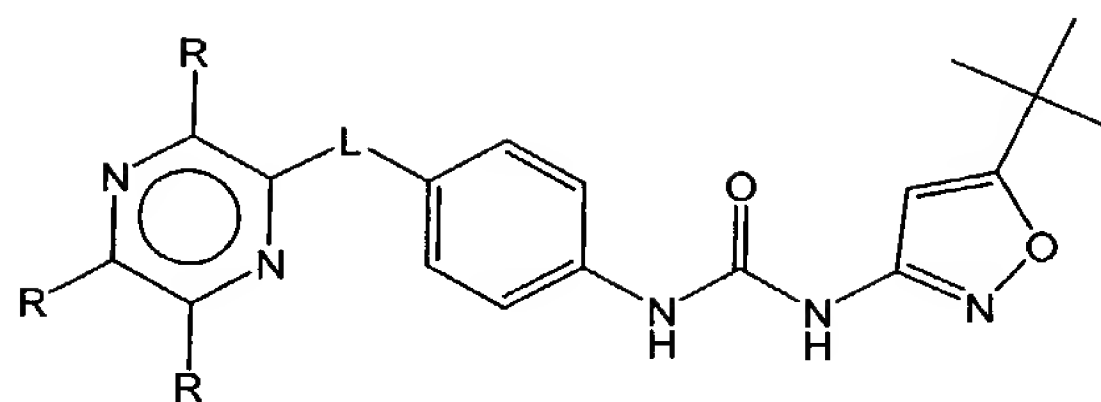
27. The compound of claim 21, corresponding to Formula (XIII):



28. The compound of claim 27, corresponding to:

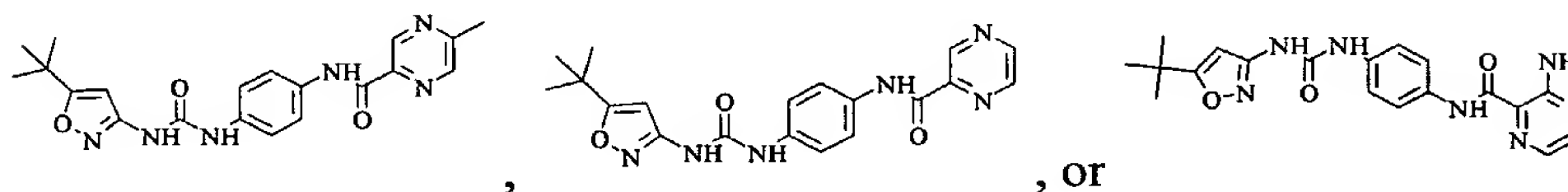


29. The compound of claim 21, corresponding to Formula (XIV):

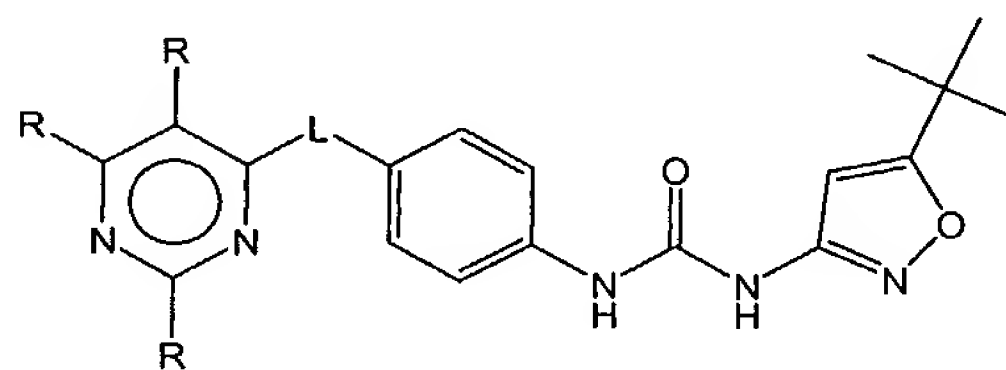


(XIV).

30. The compound of claim 29, corresponding to:

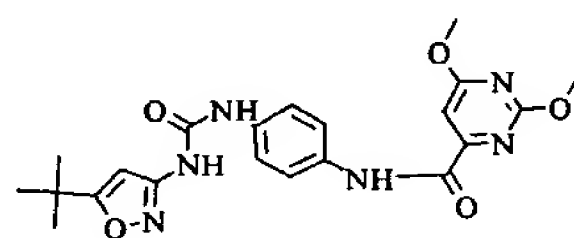


31. The compound of claim 21, corresponding to Formula (XV):

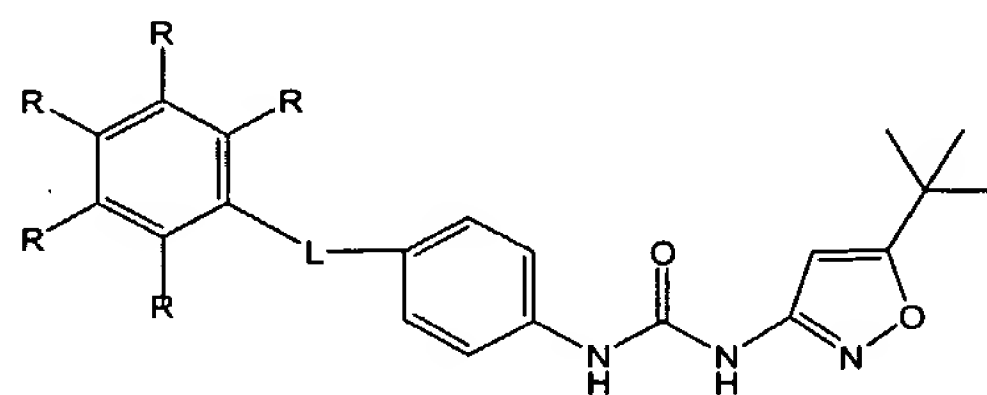


(XV).

32. The compound of claim 31, corresponding to:



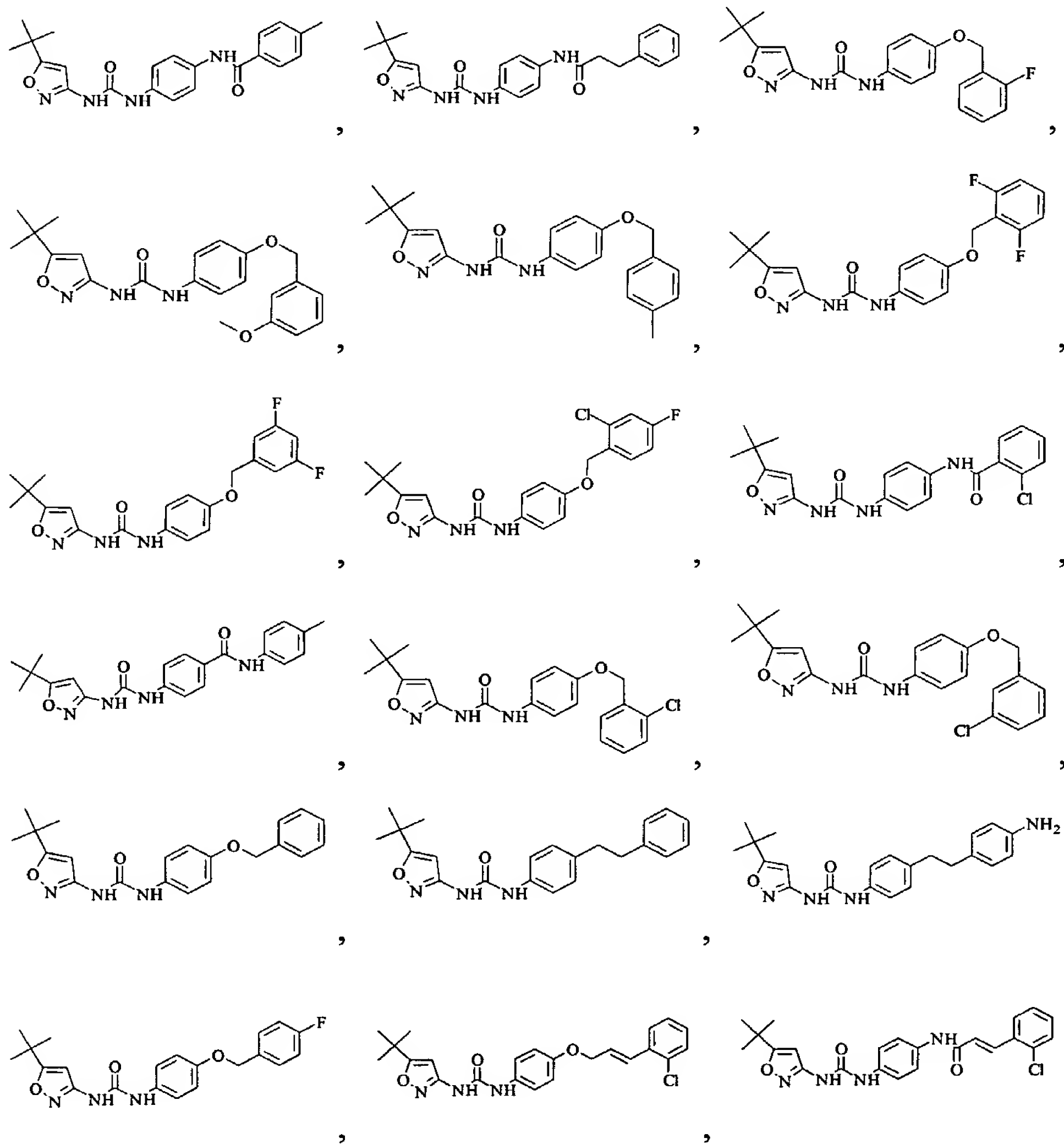
33. The compound of claim 21, corresponding to Formula (XVI):

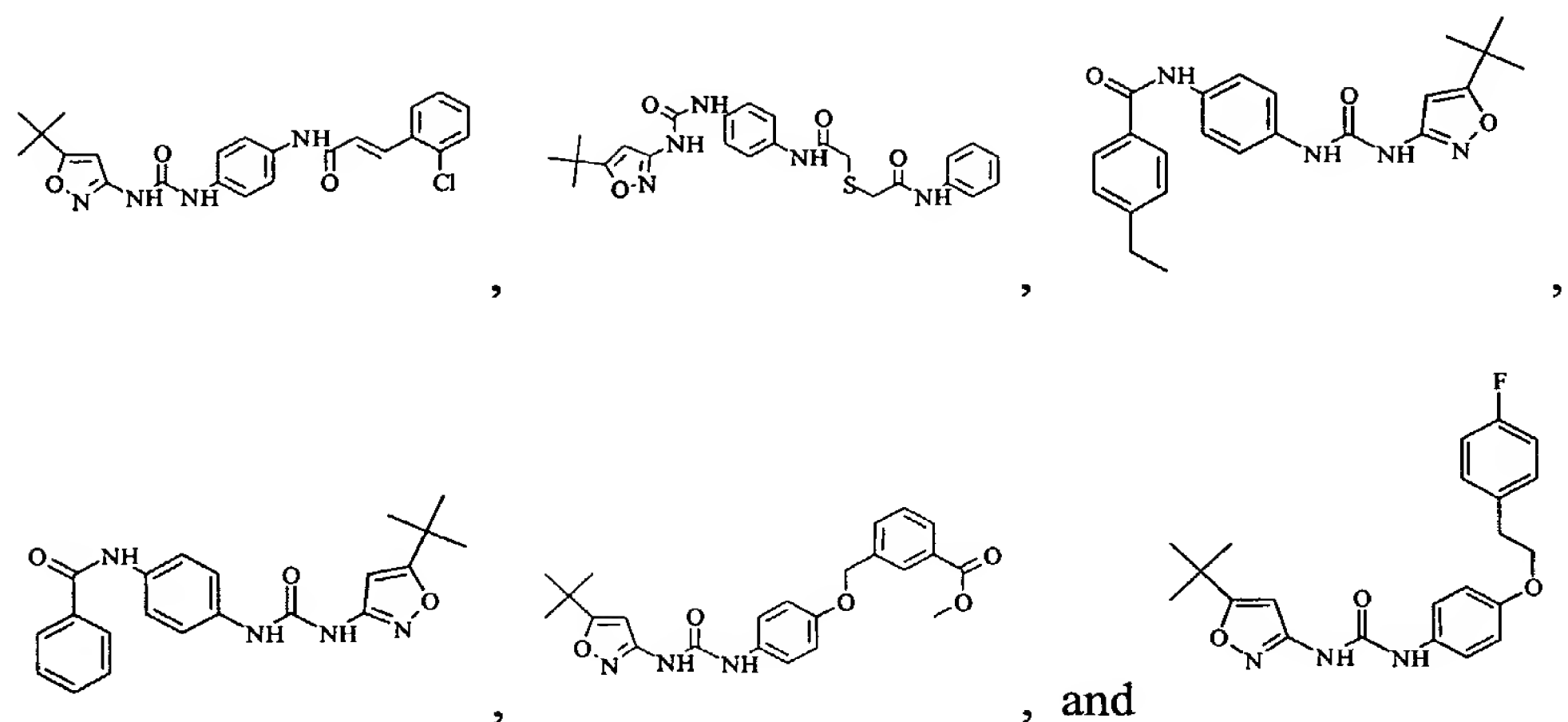


(XVI).

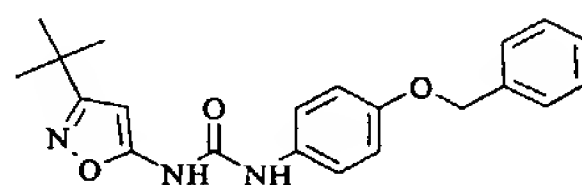
34. The compound of claim 33, wherein L is a linker selected from the group consisting of -NHC(O)-, -OCH₂-, -OCH₂CH₂-, -NHC(O)CH₂SCH₂C(O)NH-, -CHCHC(O)NH-, -CHCHCH₂O-, -CH₂CH₂-, and -CH₂CH₂C(O)NH-.

35. The compound of claim 34, selected from the group consisting of:

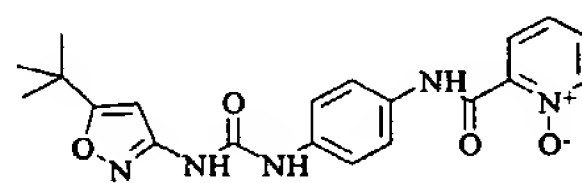




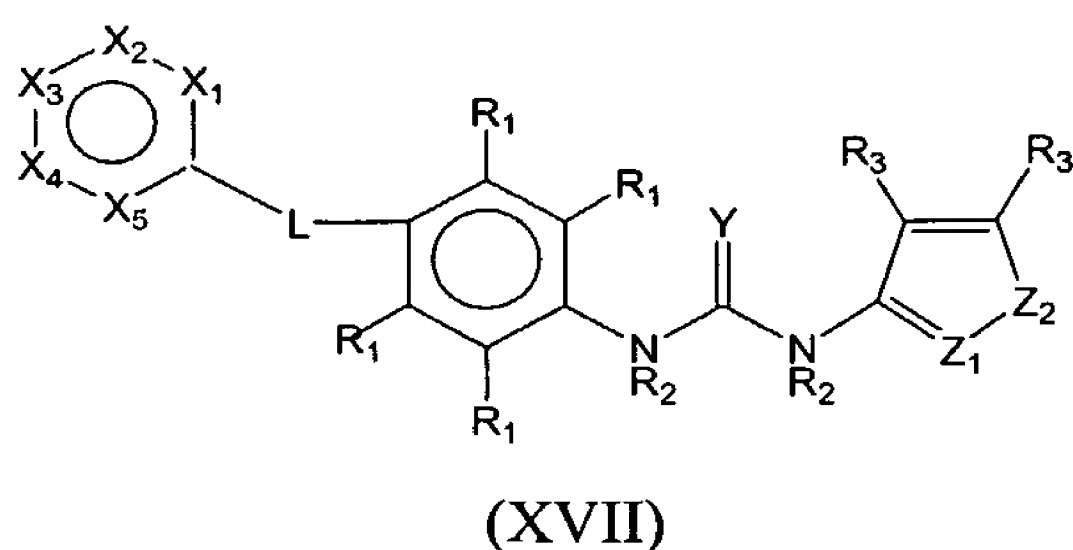
36. The compound of claim 3, corresponding to:



37. The compound of claim 5, corresponding to:



38. The compound of claim 5, corresponding to Formula (XVII):



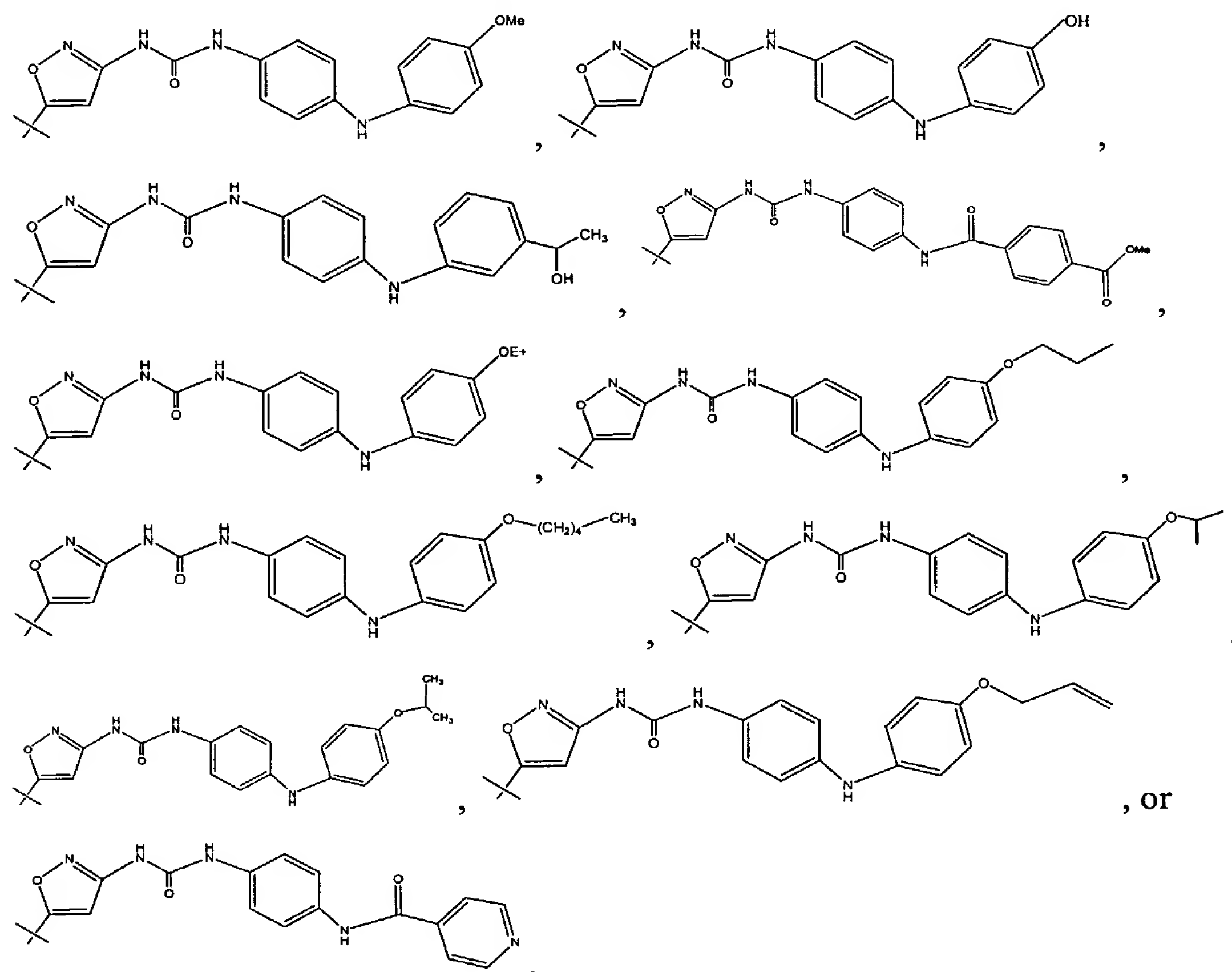
wherein:

each of X_1 - X_5 is independently C, CR, N-O, or, wherein no more than two of X_1 - X_5 is N; where

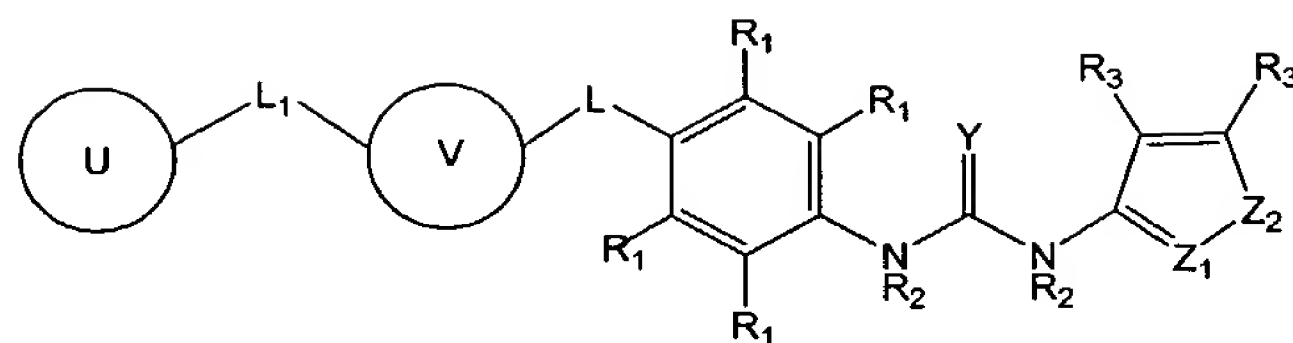
each R is independently H, halogen, substituted or unsubstituted alkyl, $-\text{OR}_d$, substituted or unsubstituted alkoxy, $-\text{OC}(\text{O})\text{R}_d$, $-\text{NO}_2$, $-\text{N}(\text{R}_d)_2$, $-\text{SR}_d$, $-\text{S}(\text{O})_j\text{R}_d$ where j is 1 or 2, $-\text{NR}_d\text{C}(\text{O})\text{R}_d$, $-\text{C}(\text{O})_2\text{R}_d$, $-\text{C}(\text{O})\text{N}(\text{R}_d)_2$ or $-\text{C}(\text{O})\text{R}_d$; or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, and

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl

with a proviso that said compound is not:

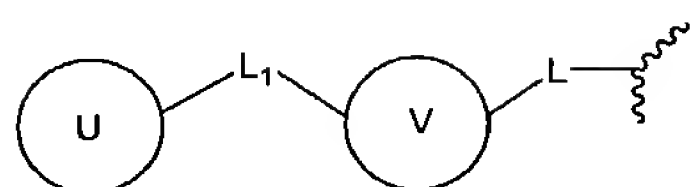


39. The compound of claim 5, corresponding to Formula (XVIII):



(XVIII)

wherein:



is selected from the group consisting of:

- (a) each of L and L₁ is independently a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -C(O)-, and -N(substituted or unsubstituted alkylene)-;

U is a substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl;
and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene;

- (b) L is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

L₁ is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, and -N(substituted or unsubstituted alkylene)-;

U is selected from the group consisting of:

- (i) substituted or unsubstituted cycloalkyl;
- (ii) unsubstituted aryl;
- (iii) aryl substituted at any position with -Cl, -I, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, -OC(O)R₃, -NO₂, -N(R_g)₂, -SR_g, -C(O)R_h, where R_h is H, -OH, -N(R_g)₂, or substituted or unsubstituted alkoxy, and where R_g is H or substituted or unsubstituted alkyl; and
- (iv) substituted or unsubstituted heteroaryl, except pyridinyl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene; and

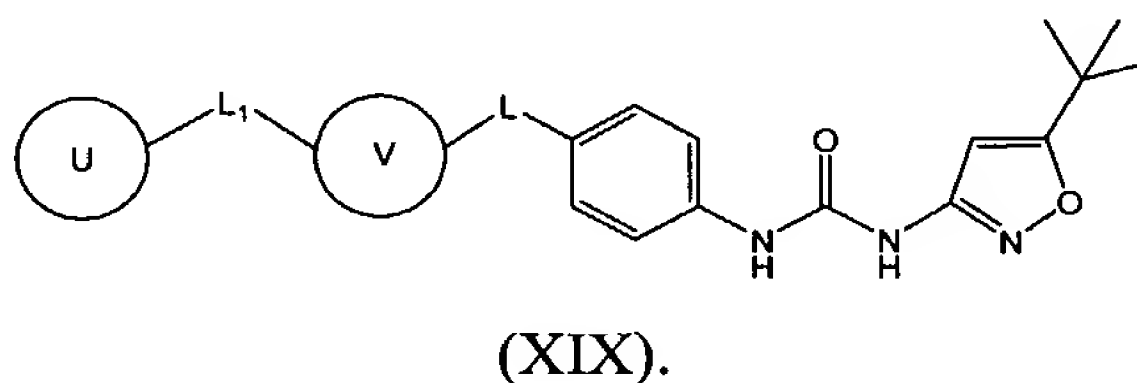
- (c) L is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

L₁ is a linker selected from the group consisting of a covalent bond, -O(substituted or unsubstituted C₂-C₅ alkylene)-, -S-, -(substituted or unsubstituted alkylene)-, -O-, -NH-, -C(O)-, -C(O)NH-, and -N(substituted or unsubstituted alkylene)-;

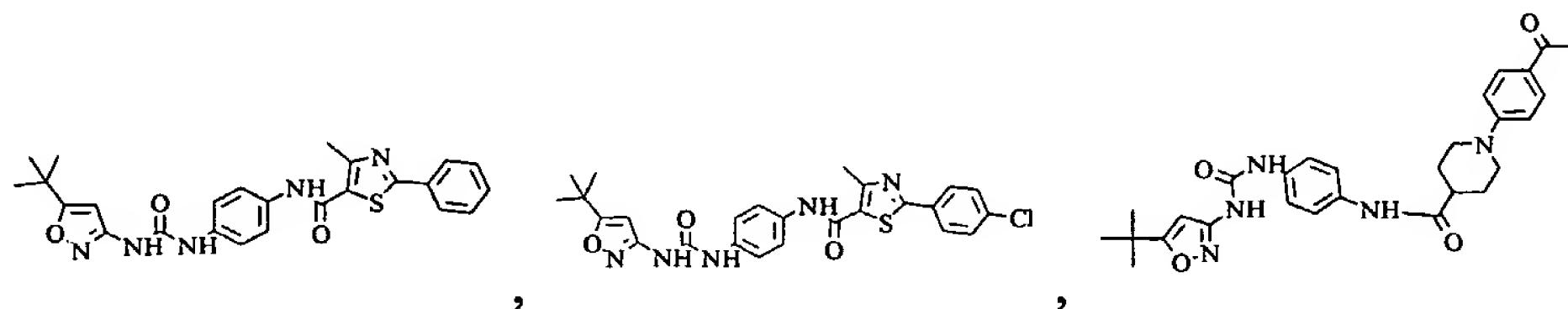
U is selected from the group consisting of substituted or unsubstituted cycloalkyl; substituted aryl; and substituted or unsubstituted heteroaryl; and

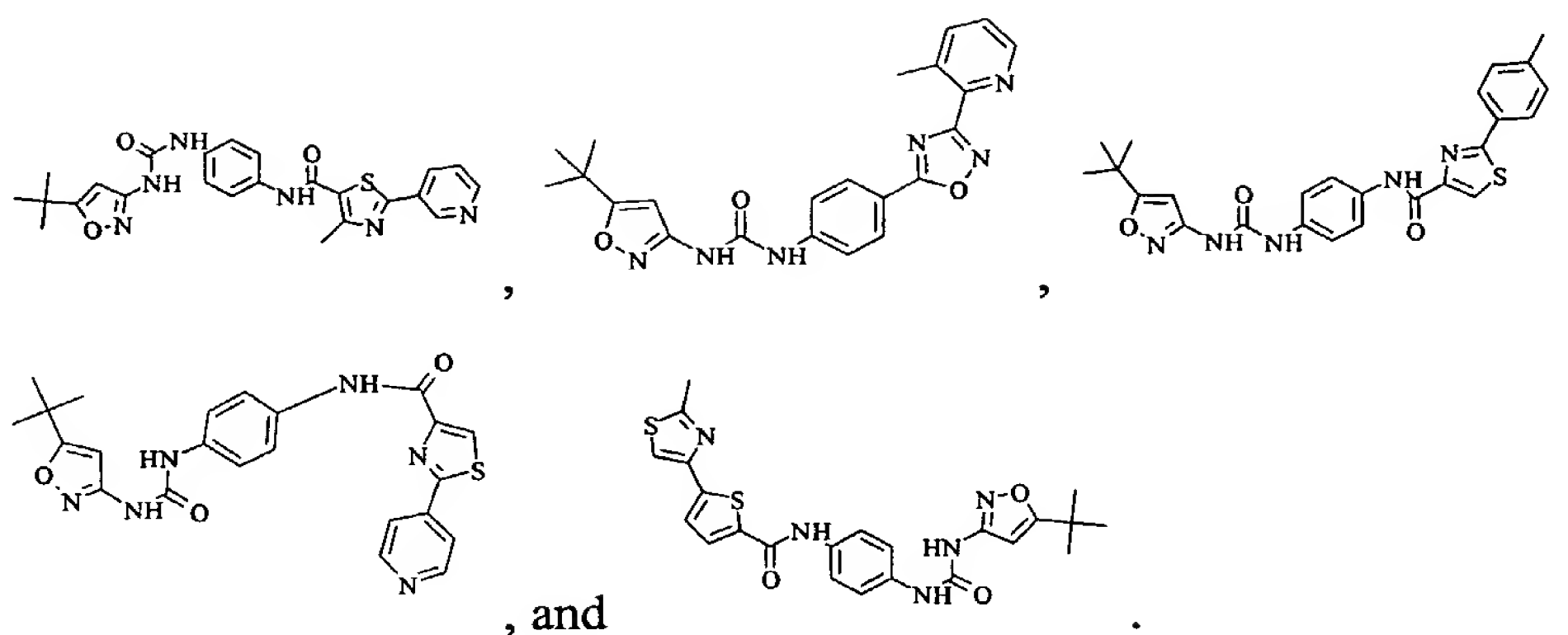
V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

40. The compound of claim 39, corresponding to Formula (XIX):

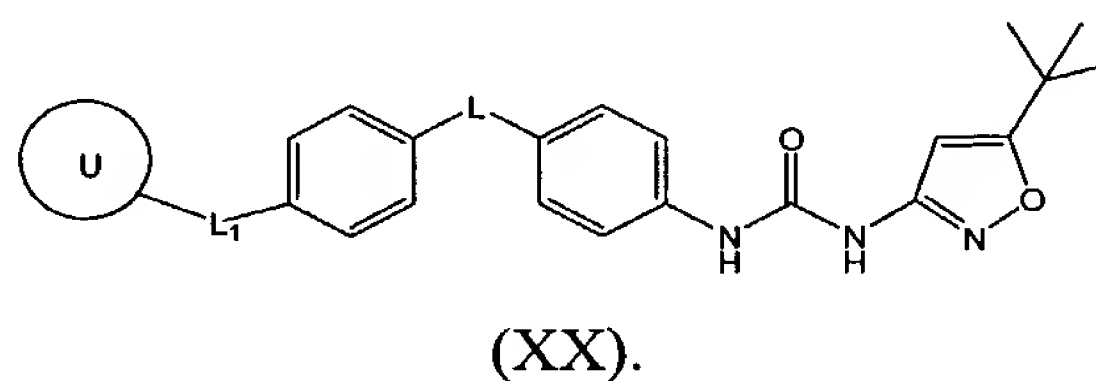


41. The compound of claim 40, wherein L₁ is a bond; and L is a bond or -C(O)NH-.
42. The compound of claim 41, wherein U is substituted or unsubstituted phenyl, thiazolyl, or pyridinyl; and V is substituted or unsubstituted piperidinylene, thiazolylene, imidazolylene, or thiophenylene.
43. The compound of claim 42, selected from the group consisting of:

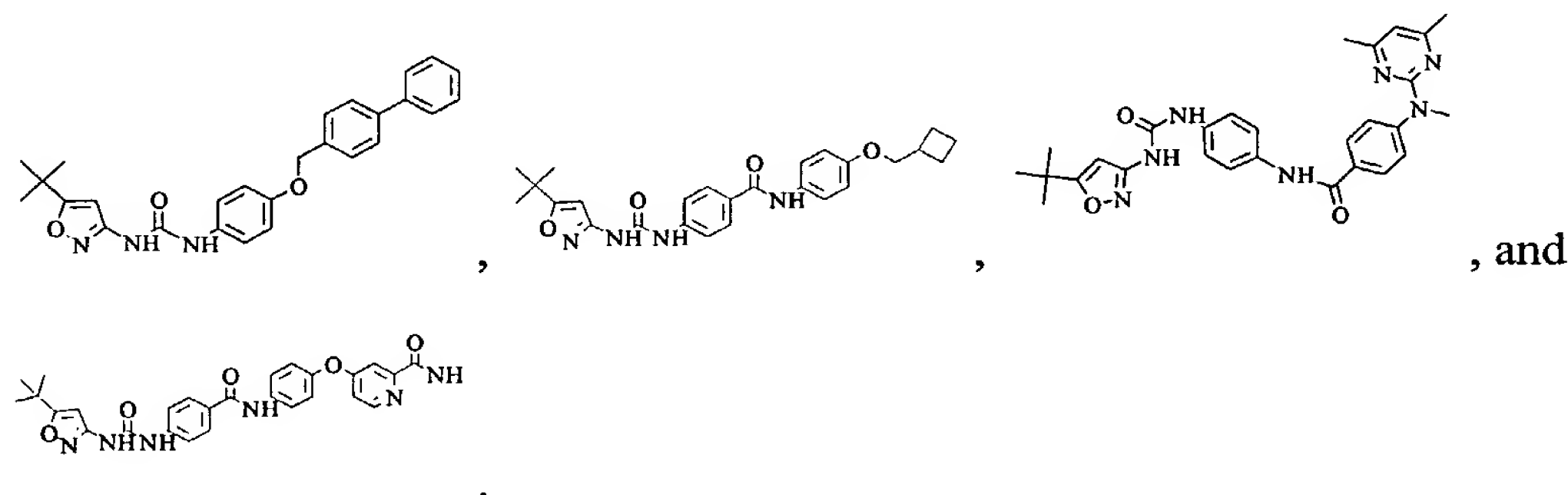




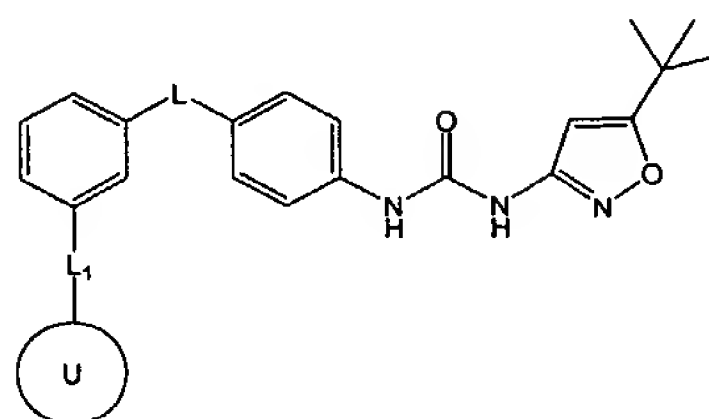
44. The compound of claim 40, corresponding to Formula (XX):



45. The compound of claim 44, wherein L_1 is a bond, $-\text{CH}_2\text{O}-$, $-\text{N}(\text{CH}_3)-$, or $-\text{O}-$; and L is $-\text{CH}_2\text{O}-$ or $-\text{NHC}(\text{O})-$.
46. The compound of claim 45, wherein U is substituted or unsubstituted phenyl, C_3 - C_6 cycloalkyl, pyrimidine, or pyridine.
47. The compound of claim 46, selected from the group consisting of:

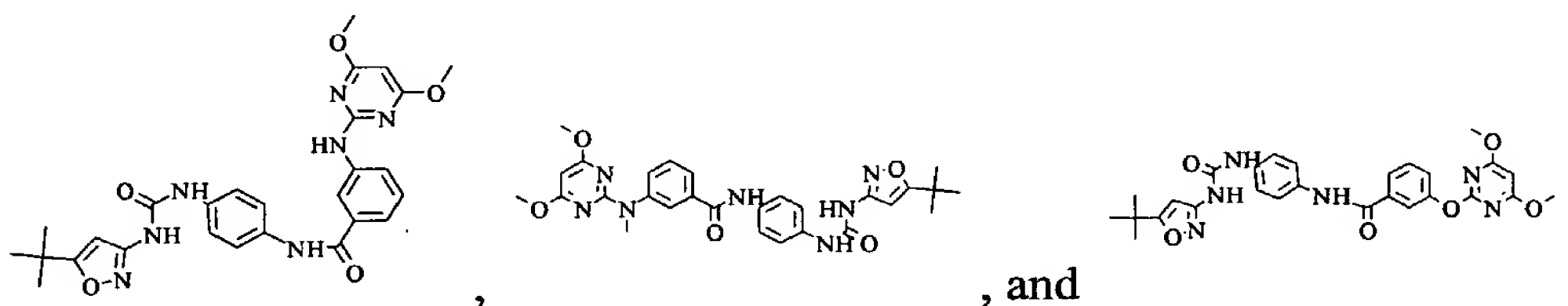


48. The compound of claim 40, corresponding to Formula (XXI):

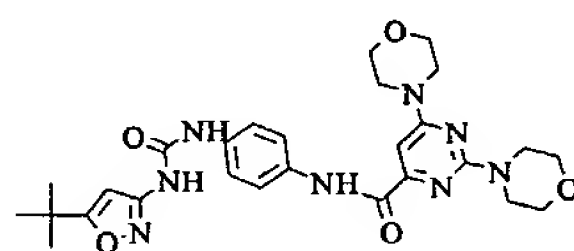


(XXI).

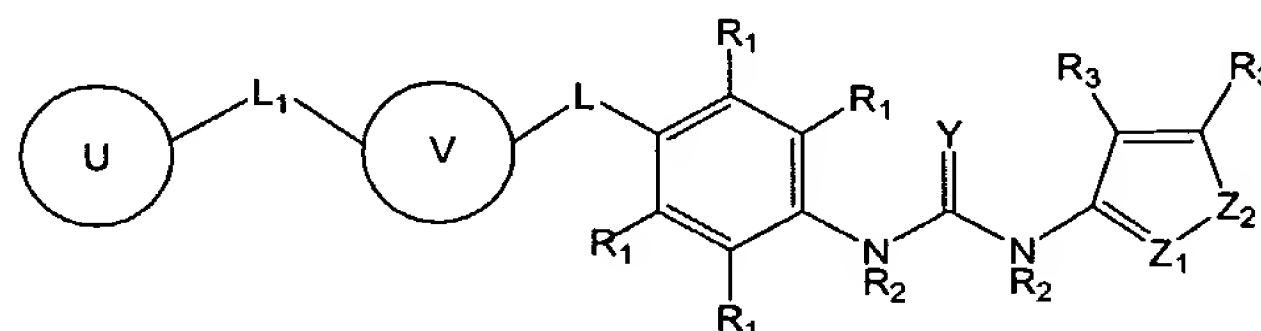
49. The compound of claim 48, wherein L_1 is a $-NH-$ or $-O-$; and L is $-NHC(O)-$.
50. The compound of claim 49, wherein U is substituted or unsubstituted pyrimidyl.
51. The compound of claim 50, selected from the group consisting of:



52. The compound of claim 40, corresponding to:



53. The compound of claim 5, corresponding to Formula (XXII):



(XXII)

wherein:

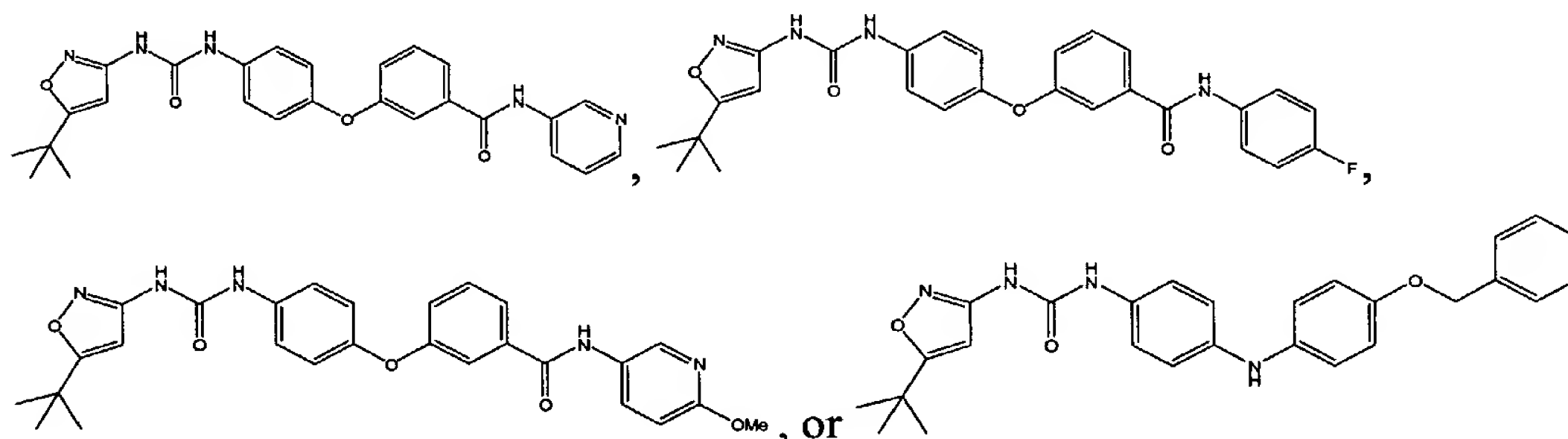
L_1 is a linker selected from the group consisting of a covalent bond, $-(\text{substituted or unsubstituted alkylene})-$, $-(\text{substituted or unsubstituted alkenylene})-$, $-O-$,

-O(substituted or unsubstituted alkylene)-, -C(O)-, -C(O)(substituted or unsubstituted alkylene)-, -C(O)(substituted or unsubstituted alkenylene)-, -NH-, -NH(substituted or unsubstituted alkylene)-, -NH(substituted or unsubstituted alkenylene)-, -C(O)NH-, -C(O)NH(substituted or unsubstituted alkylene), -C(O)NH(substituted or unsubstituted alkenylene)-, -NHC(O)(substituted or unsubstituted alkylene)-, -NHC(O)(substituted or unsubstituted alkenylene)-, -S-, -S(substituted or unsubstituted alkylene)-, and
 -NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH-;

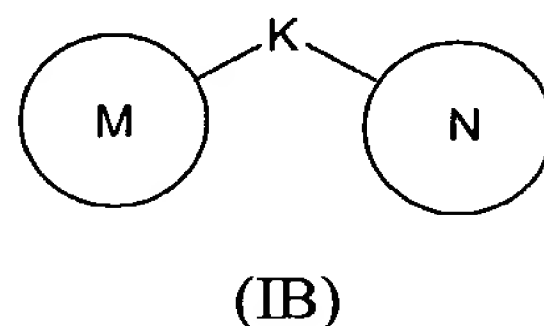
U is a substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene;

with a proviso that said compound is not:



64. A method of modulating a kinase, said method comprising administering an effective amount of a compound corresponding to Formula (IB):

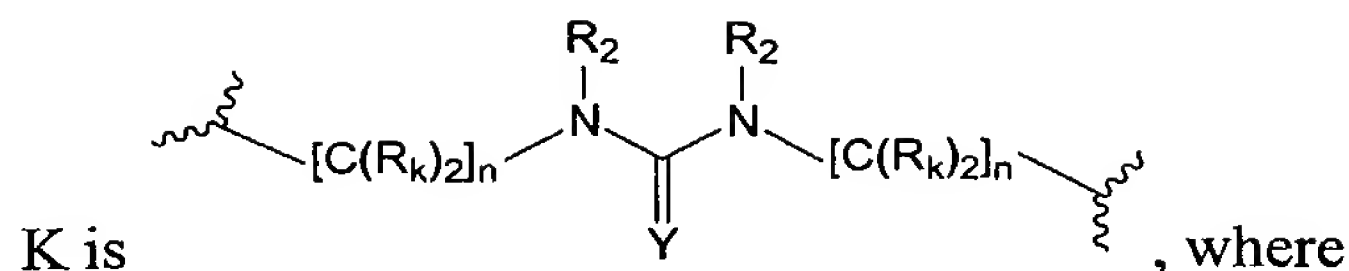


wherein:

M is a substituted or unsubstituted heteroaryl or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

and



Y is O or S;

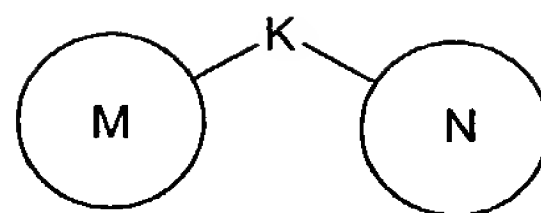
each R_k is independently H, halogen, substituted or unsubstituted alkyl, -OH, substituted or unsubstituted alkoxy, $-\text{OC}(\text{O})R_d$, $-\text{NO}_2$, $-\text{N}(\text{R}_d)_2$, $-\text{SR}_2$, $-\text{C}(\text{O})R_d$, $-\text{C}(\text{O})_2R_d$, $-\text{C}(\text{O})\text{N}(\text{R}_d)_2$, or $-\text{N}(\text{R}_d)\text{C}(\text{O})R_d$, where each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 's are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

65. The method of claim 64, wherein said kinase is c-kit.
66. The method of claim 64, wherein said kinase is abl.
67. The method of claim 64, wherein said kinase is p38.
68. The method of claim 64, wherein said kinase is MKNK2.
69. The method of claim 64, wherein said kinase is flt-3.
70. The method of claim 64, wherein said kinase is PDGFR.
71. The method of claim 64, wherein said kinase is STK-10.
72. A method of treating a cellular proliferative disorder, said method comprising administering a therapeutically effective amount of a compound, or pharmaceutically acceptable salt thereof, corresponding to Formula (IB):



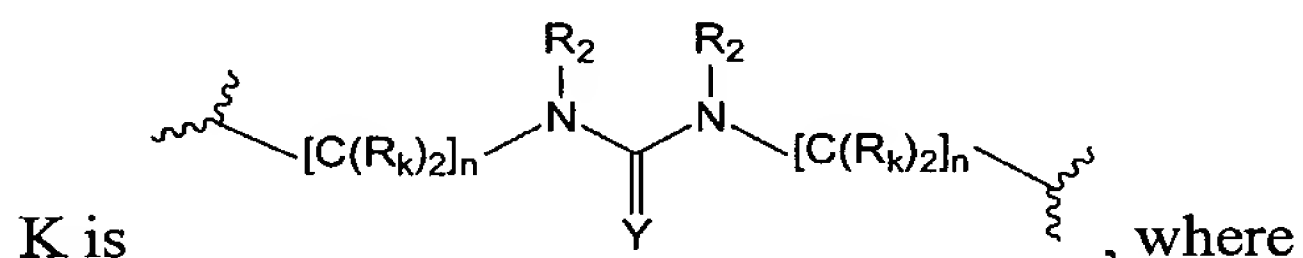
(IB)

wherein:

M is a substituted or unsubstituted heteroaryl or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

and



Y is O or S;

each R_k is independently H, halogen, substituted or unsubstituted alkyl, -

OR_d , substituted or unsubstituted alkoxy, $-OC(O)R_d$, $-NO_2$, $-N(R_d)_2$,

$-SR_d$, $-C(O)R_d$, $-C(O)_2R_d$, $-C(O)N(R_d)_2$, or $-N(R_d)C(O)R_d$, where each

R_d is independently H, substituted or unsubstituted alkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted

or unsubstituted heteroaryl;

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl,

substituted or unsubstituted aryl, or substituted or unsubstituted

heteroaryl; or wherein two R_2 groups are linked together by an

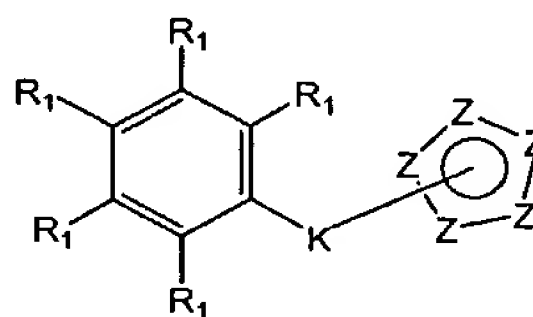
optionally substituted alkylene; and

each n is independently 0, 1, 2, 3, or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer

pharmaceutically acceptable salt or solvate thereof.

73. The method of claim 72, wherein said compound corresponds to Formula (IA):



(IA)

wherein:

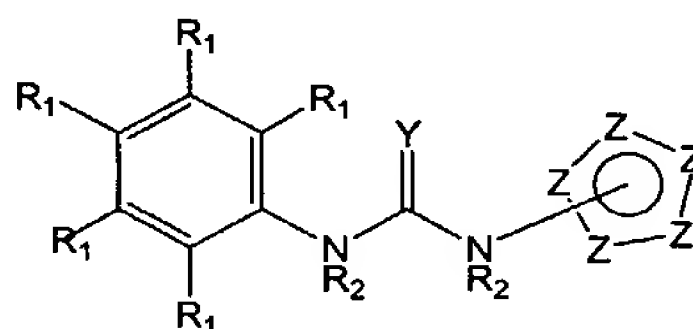
each Z is independently C, CR₃, N, NR₃, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

where R₃ is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

each R₁ is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR_c, -OC(O)R_c, -NO₂, -N(R_c)₂, -SR_c, -S(O)_jR_c where j is 1 or 2, -NR_cC(O)R_c, -C(O)N(R_c)₂, -C(O)₂R_c, or -C(O)R_c; or two adjacent R₁'s, are taken together to form a substituted or unsubstituted aryl or heteroaryl,

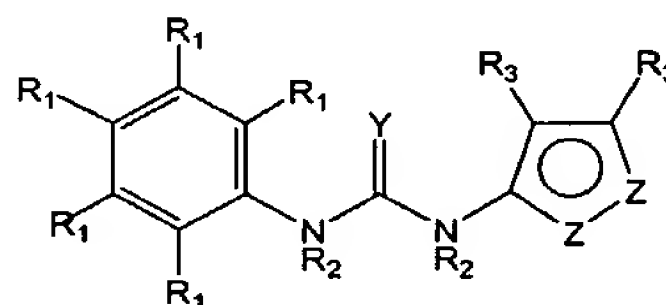
each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

74. The method of claim 73, wherein said compound corresponds to Formula (I):



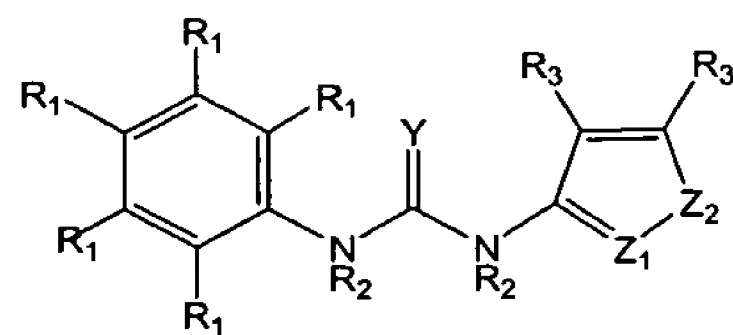
(I).

75. The method of claim 74, wherein said compound corresponds to Formula (II):



(II).

76. The method of claim 75, wherein said compound corresponds to Formula (III):



(III)

wherein Z₁ is CR₃ or N; and Z₂ is O or S.